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"Q" FEVER, A NEW FEVER ENTITY: CLINICAL FEATURES, DIAGNOSIS AND LABORATORY INVESTIGATION.

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Introduction.

IN August, 1935, the occurrence of a number of cases of fever among workers in a large meatworks in Brisbane was brought to the notice of the Director-General of Health and Medical Services for Queensland, Sir Raphael Cilento, who directed me to investigate the matter. It appeared that the cases which incited the inquiry had begun to occur early in 1933. Since then there had been about 20 cases—not indeed a large number among 800 employees. Most of the cases resembled in a general way the nine cases to be described in this paper. The type of fever was a continued one of seven to twenty-four days' duration. There were certain features about the cases which caused the medical attendants to believe that they constituted a distinct clinical entity. The most outstanding feature was the uniform failure of blood cultures and agglutination tests to throw light on the diagnosis.

Further cases have occurred from time to time, and the courtesy of many practitioners has enabled me to investigate them directly. When the inquiry began, a number of diseases came to mind as possible causes: typhus, which in several forms is endemic in Queensland; undulant fever, a recognized

occupational disease of meat workers; aberrant typhoid and paratyphoid fevers; and leptospirosis. All the tests for these, however, gave negative results. The commoner animal diseases were next considered and excluded. Then the suspicion arose and gradually grew into a conviction that we were here dealing with a type of fever which had not previously been described. It became necessary to give it a name, and "Q" fever was chosen to denote it until fuller knowledge should allow a better name.

One line of investigation, guinea-pig inoculation, has been particularly fruitful. Guinea-pigs acquire the disease readily by injection of blood or urine from a patient. Their subsequent immunity permits a specific diagnosis to be made, and has rendered it possible to prove that "Q" fever is a pathological as well as a clinical entity.

As no organism could be seen in or cultivated from human or guinea-pig material, it appeared likely that the infecting agent was a virus. Infected guinea-pig liver was thereupon sent to Dr. F. M. Burnet, of Melbourne, who, transferring the infection to mice, was successful in discovering rickettsial bodies in their spleens.

As the work proceeded, its scope had to be extended. Cases of fever of doubtful causation were found to occur from time to time in and around Brisbane apart from meat workers. When these were investigated some of them proved to be due to "Q" fever. The cases now to be described include, therefore, in addition to five from the abattoir, two from other parts of Brisbane, one from Gympie and one from Pomona.

While much about the disease is still obscure, the time is ripe for a general review of present knowledge.

Clinical Features.

Nine cases of illness have been proved to be "Q" fever by guinea-pig inoculation and immunity tests. The number is small, but it is hoped that from them an idea of the clinical picture of the disease may be obtained. A general description will be given here, and the details of the cases in the next section.

The patients were all men; their ages were 50, 29, 45, 18, 17, 37, 36, 33 and 55 years.

Incubation Period.

In Case VI the incubation period could be deduced as fifteen days or less.

Onset.

The onset of the illness in all cases was acute. Within a few days of the first premonitory symptoms the victims were in bed quite ill. The first complaints were usually malaise, anorexia, headache, pains in the back and limbs, and feverishness.

Course of the Illness.

As the illness developed, the symptoms became more severe and the general condition of the patient worse. The headache was troublesome and persistent, and often interfered with sleep. The face was flushed or pale, the eyes were closed and the tongue was coated. In the more severe infections the patient became drowsy, even stuporose, and passed on into a typhoid state. The symptoms gradually abated as the temperature fell. With those patients running the shorter course the improvement, once it started, was rapid.

Fever.

The temperature rose rapidly and remained high. The daily maxima were usually between 39° and 40° C. (102° to 104° F.). Some of the charts show large daily remissions. These may be due in part to the use of antipyretic drugs for the relief of headache, but this may not explain them all. The course of the fever varied considerably. There were two fairly distinct types. In Cases II (Figure II), IV (Figure IV), V and VI the fever lasted from six to nine days. Its subsidence was rapid, Case II showing a definite crisis. These cases had much the same type of fever as that characteristic of urban or murine typhus.

In other cases the course was more prolonged, with a gradual defervescence. In Case I (Figure I) the primary fever lasted fourteen days, and after two days' interval there was a relapse lasting another eight days. In Case III (Figure III) there were at least seventeen days of fever, and in Case IX (Figure VI), twenty-four days. The course in Case VII (Figure V) was extremely prolonged. The fastigium of the fever lasted till the twenty-third day, and the fall thereafter was very gradual, so gradual that one could not decide the precise day of ending. There was still a slight evening rise of temperature in the ninth week.

Pulse Rate.

One of the features of these cases was the slow rate of the pulse at the beginning of the illness in comparison with the height of the fever. This is shown well in Figure VI, in which the pulse rate curve hardly leaves the base line, and in Figures II and III. Case VII was the only one in this series in which the pulse rate exceeded 100 to any great extent. The slow pulse rate is of some help in the diagnosis, but its value is limited by the occurrence of a slow pulse rate also in typhoid and typhus fevers and in Weil's disease.

Headache.

The outstanding symptom was headache. It was present in every case but one, and was the chief complaint of most of the patients. The terms severe, intense and raging were used in the notes to describe it. It often persisted for some days after admission of the patient to hospital, and called for special treatment.

Shivers and Sweats.

Four patients noticed shivers at the onset. Two patients had a rigor, one on the third and the other on the seventh day of illness. Some had profuse sweating at night. This may have been due in part to the headache drugs.

Rash.

A rash is not a feature of "Q" fever. Six of the nine patients had no sign of a rash. In Cases I and VIII a few indefinite red spots were found when the abdomen was examined at the time of the patient's admission to hospital. They would hardly have been thought worthy of record except for the endeavour to make a clinical diagnosis. Only one of the nine, Patient VII, had a definite rash. It appeared on the fourteenth day of illness as a punctate red rash, first on the back, then on the chest and abdomen. It had partly faded by the next morning and had gone the morning after.

The absence of a characteristic rash during the first week in "Q" fever is of importance in distinguishing the disease from urban typhus. The occasional case of typhus that occurs in Brisbane almost always has a well-marked rash which appears about the fifth day and is a striking feature of the illness. It is to be borne in mind, however, that there are atypical cases of fever belonging to the typhus group, particularly in certain places, which run their course without a rash.

Jaundice.

Only one patient in this series became jaundiced. This was number VII, the most severely affected of them all. The jaundice appeared on the thirteenth day of the illness, deepened during the next week, and disappeared in another ten days. Its presence raised a problem in diagnosis which is discussed later.

Conjunctival Congestion.

One patient (number I) had severe congestion of the conjunctivæ, which lasted till at least the eleventh day. The associated photophobia continued throughout the illness. At least one other patient had bloodshot eyes at the onset. Photophobia was a prominent symptom.

Congestion of the conjunctivæ is regarded, and rightly so, as a valuable help in the differential diagnosis of the leptospiroses. "The injection of the conjunctivæ is almost pathognomonic" (Manson-Bahr[1]). The presence of this sign in two of our cases of "Q" fever, as well as its occurrence in various types of typhus fever, is a reminder that it is not an absolute sign of a leptospirosis.

The Spleen.

In none of the nine cases was the spleen recorded as definitely palpable. This was surprising, for infected guinea-pigs and mice invariably have enlarged spleens; and in the series of cases of undiagnosed fever in abattoir workers previous to the occurrence of these nine, many of whom must have had "Q" fever, about a quarter had palpable spleens. I feel that the spleen must be enlarged to some extent in human cases of "Q" fever, and that in a more extensive series it would sometimes be found large enough to be palpated.

The Blood.

Blood examinations were made in four cases (Table I). In one case there was a definite anæmia. In each of the examinations the total of the white cells was within normal limits. In three cases there was a relative and absolute lymphocytosis. In two of these the counts that disclosed the lymphocytosis were made after the temperature had fallen to normal.

Other Signs and Symptoms.

Vomiting was present in three cases; in two it was persistent. Two patients had some abdominal distension. Constipation was the rule. No patient had diarrhœa. Two had a slight cough. Three had epistaxis; in one of them it was severe and repeated. At the beginning of the illness albuminuria was found almost invariably, clearing up before long. The finding of granular casts in the urine is recorded twice. Enlargement of lymph glands was not noticed in any case.

TABLE I.

"Q" Fever Cases, Blood Examinations.

Case Number.	Day of Illness.	Red Cells.		Hæmoglobin. Percentage.	White Cells.					
		Number per Cubic Millimetre.	Appearance.		Number per Cubic Millimetre.	Neutrophile Cells.		Lymphocytes.		Eosinophile Cells. Percentage.
						Percentage.	Total.	Percentage.	Total.	
1	5 26	4,480,000 4,490,000	Anisocytosis. Anisocytosis.	88 88	9,300 6,300	74 62	6,882 3,906	26 38	2,418 2,394	
2	10	5,300,000	Normal.	104	5,700	35	1,995	65	3,705	
4	14	5,040,000	Normal.	100	8,900	38	3,382	61	5,429	1
7	11 23 32	3,600,000	Hypochromia, polychromasia, slight basophilia.	67	9,000 8,500	56 68 46	5,040 5,780	44 32 54	3,960 2,720	

These examinations were made by the staff of the pathological laboratories of the Brisbane General Hospital and the Mater Misericordiæ Public Hospital, and are quoted by courtesy of Dr. J. V. Duhig and Dr. G. Taylor.

Convalescence.

During convalescence the strength and sense of well-being returned at varying rates. Those patients whose fever had run the shorter course improved rapidly after it was over. Some of them returned to work as soon as 16, 18 and 20 days after the illness began. In others the restoration to health was slower. Patient VII was still away from work after five months, the convalescence being delayed by anæmia, corneal ulcer and neck stiffness. Individual patients complained of "nerves", pain in the thigh, numbness in the hand, insomnia and thinning of the hair, as well as of the general weakness and weakness of the legs which are to be expected after a serious illness.

Case Histories.

In these cases, following Osler's practice in discussing typhoid fever, I have taken the day on which the patient went to bed, as far as that information could be accurately obtained, as the first day of the illness. It is necessary to make this definition, as frequent reference will be made to the day of illness on which events occurred. If the illness was to be counted from the day of the first symptom, the duration would be several days longer.

Case I.

The notes of Case I are published by courtesy of Dr. L. A. Little and Dr. P. J. Kelly.

G.N., aged fifty years, a worker among hides at the abattoir, was admitted to the Mater Misericordiæ Public Hospital on September 14, 1935. He said that he had been ill about a week with headache, shivers, pains across the back and in various places. He remained at work, however, until September 12, which date I have taken as the beginning of the illness. At the time of his admission to hospital there was a severe congestion of the conjunctivæ with photophobia. The tongue was coated. The abdomen was slightly distended and showed a number of small red spots of doubtful significance. They disappeared in the course of a few days. The spleen was not palpable at the time of admission. A few crepitations were heard at the base of the right lung.

The fever was of a remittent type and terminated by lysis, the primary fever lasting fourteen days (Figure I).

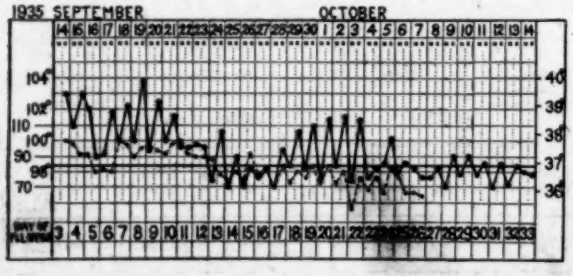

FIGURE I.
Chart of G.N. (Case I). Continuous line = temperature; broken line = pulse rate.

After two days' interval there was a relapse lasting eight days, and even after this there was a tendency for the temperature to rise slightly in the evenings. The pulse was comparatively slow during the fever, the rate never exceeding 100. The patient was quite ill for a time, drowsy, and lying in a typhoid state. His condition improved somewhat as the temperature fell the first time, and more definitely when the relapse was over. No signs were found in lungs or kidneys or elsewhere to explain the secondary fever. The conjunctivitis was troublesome till at least the eleventh day, and there was still some photophobia on the twenty-ninth day. The patient sat up on October 26 and was discharged from hospital on November 3.

Blood taken on the third day of illness was injected into a guinea-pig which probably acquired "Q" fever. Urine was injected into guinea-pigs on the twelfth and twenty-ninth days. Both samples contained the infecting agent, and the strain obtained from the latter sample was continued through sixteen passages in guinea-pigs.

Case II.

The notes of Case II are published by courtesy of Dr. E. G. Thomson and Dr. C. Shellshear.

F.L., aged twenty-nine years, meat inspector, examining mutton and beef, became ill on September 7, 1935, with headache, lumbar backache, shivers, and cough with a little phelgm. There was some loss of weight. His bowels were constipated (as usual). He was admitted to the Brisbane General Hospital on September 13. The headache was still present and was his chief complaint. The skin was pale and moist, the tongue thickly furred, but raw at the tip. There were a few rhonchi in the lungs and a doubtful area of dulness at the right base.

The fever remained high till the ninth day of illness, when it terminated with a crisis (Figure II). The pulse rate at no time exceeded 100. The respiratory rate was practically normal. The patient's general condition improved rapidly with the fall of the temperature. He was discharged from hospital on September 21, and, though not quite well, resumed work on September 25.

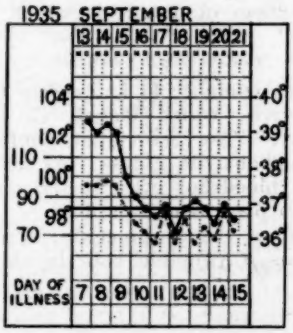

FIGURE II.
Chart of F.L. (Case II). Continuous line = temperature; broken line = pulse rate.

The infecting agent was not obtained from urine tested on the eleventh day of illness, but was obtained from urine on the twenty-eighth day, that is, the nineteenth day after the fever was over, and over a week after the return to work.

Case III.

The notes of Case III are published by courtesy of Dr. V. Beresford Taylor.

A.M., aged forty-five years, dairy farmer, near Brisbane, first felt ill on November 24, 1935. Next morning he delivered some milk, but went to bed in the evening with a raging headache and a temperature of 38·9° C. He was admitted the next day to a private hospital. The headache was intense, sometimes frontal, sometimes occipital. It continued till the seventh day. The spleen was not palpable. There was no rash.

The temperature was high for eight days, then fell by lysis (Figure III). The large remissions may have been

due to the use of drugs to relieve the headache. The pulse rate was comparatively slow, only once exceeding 96. The patient left hospital on the nineteenth day, still inclined to have a slight evening rise of temperature, but improving daily in his general condition. Insomnia was a trouble throughout, even persisting into convalescence.

On the fourth day of the illness blood was inoculated into a guinea-pig, a mouse and a rabbit. The guinea-pig acquired the infection and it was continued through eleven passages in guinea-pigs. The mouse became quite ill on the eighth day and had a subnormal temperature, and then recovered. The rabbit showed no definite effect. A guinea-pig injected with urine on the same day was unaffected. This sample of urine showed a cloud of albumin and a trace of acetone, and on microscopic examination numerous granular casts.

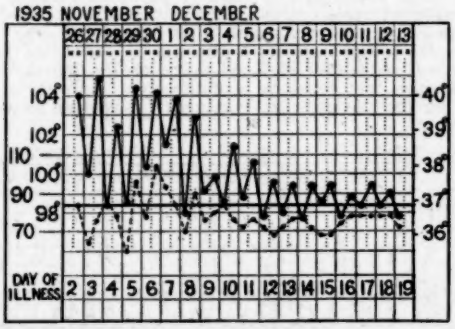

FIGURE III.
Chart of A.M. (Case III). Continuous line = temperature; broken line = pulse rate.

Case IV.

The notes of Case IV are published by courtesy of Dr. A. W. St. Ledger and Dr. P. J. Kelly.

E.K., aged eighteen years, a worker on the beef slaughter floor at the abattoir, became definitely ill on February 11, 1936, with pains in the legs, arms and lumbar region, headache and nausea. There had been lassitude for the previous two days. There was some vomiting and a slight cough. He was admitted to the Mater Misericordiæ Public Hospital on February 15, as his condition was not improving. He was then fairly ill.

The vomiting and the lumbar pain continued for a few days more. After that improvement was rapid. The temperature came down quickly (Figure IV). Except on

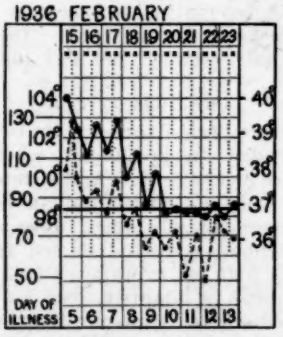

FIGURE IV.
Chart of E.K. (Case IV). Continuous line = temperature; broken line = pulse rate.

the day of the patient's admission to hospital the pulse was comparatively slow. The urine showed no abnormality. He was discharged from hospital on March 4 and went back to work on March 30.

Blood taken on the ninth (and last) day of fever was injected into a guinea-pig. This animal acquired a latent infection which became obvious on passage. Another sample of blood taken on the fourteenth day of illness (that is, the fifth day of convalescence) and two samples of urine passed during convalescence all failed to infect guinea-pigs.

Case V.

The notes of Case V are published by courtesy of Dr. A. J. Lynch.

J.J., aged seventeen years, beef gutter, became ill on May 9, 1936. There had previously been feverishness, nausea and lassitude for three days, but not of sufficient degree to prevent his working. The head ached severely for several days after the onset. There were weakness, giddiness and loss of appetite. The eyes became bloodshot and could hardly be opened. The face was flushed, the tongue very dirty. The temperature rose and continued high, reaching 40° C. on several occasions. It became normal on May 17. The pulse rate kept at about 90 during the fever. There was no rash. The spleen was not palpable. The patient resumed work on May 25.

The virus was obtained by guinea-pig inoculation of blood taken on the fifth day of illness, and the infection has been continued through thirty passages in guinea-pigs. Guinea-pigs injected with urine on three occasions remained unaffected. Another sample of blood was taken four months after the illness for agglutination tests.

Case VI.

The notes of Case VI are published by courtesy of Dr. R. Malcolm.

J.C., aged thirty-seven years, mutton slaughterman, noticed an "influenza" feeling and pain in the back first on May 10, 1936. He continued to work, however, till May 12. There was a fairly high temperature, at about 38·7° C., for four days, with sweats each night. The pulse was comparatively slow. There were no spots and no epistaxis. On the morning of May 16 the temperature had fallen to 37·2° C., the headache was less severe, and the tongue, although dry, was beginning to clear. There was a big sweat the same night. The temperature was quite normal on May 18. He returned to work on June 1.

A guinea-pig was injected with blood on the third day of illness and developed "Q" fever; another was injected with urine on the eighth day without result.

This patient had had two rather similar febrile attacks in the previous four months. In view of the immunity conferred on a guinea-pig by one attack of "Q" fever, it is likely that the previous attacks were due to other causes. The patient had returned to work on Monday, April 27, after a fortnight at the seaside. This permits an estimation of the incubation period as fifteen days or less.

Case VII.

The notes of Case VII are published by courtesy of Dr. E. R. Row and Dr. A. Murphy.

M.D., aged thirty-six years, braceman employed on new sewerage construction, became ill on August 30, 1936, with malaise and pains and aches all over, especially round the hips. Next day he was feverish and had shivers. The following day he began to vomit and vomited two or three times a day for the next week. The bowels were costive. There was no headache and no dysuria. There was a slight cough.

He was admitted to the Brisbane General Hospital on September 8. His temperature was then 39·6° C., his pulse rate 104. He was lethargic, his face was flushed, his tongue was furred and moist. The abdomen was slightly distended. On September 10 there was a very severe epistaxis. The nose was packed and ten mils of Congo red solution were given intravenously. Next day jaundice

appeared and became deep during the following week. All this time the patient was very ill, very drowsy, semi-delirious, hiccupping, and incontinent of urine and faeces. The liver was definitely enlarged, but the spleen was not palpable at any time. On September 12, the fourteenth day of the illness, a punctate red rash came out on the back, then on the chest and abdomen. It had partly faded by the next morning and had gone on September 14. On September 16 he was given ten mils of calcium gluconate solution intramuscularly, and next day 0·9 gramme of sodium thiosulphate intravenously.

On September 18, the twentieth day of illness, there was a definite improvement in the general condition and the jaundice was less. It had practically disappeared in another ten days. After the twenty-third day the temperature came down very gradually, becoming apparently normal on the thirty-ninth day. (See Figure V.) A slight degree of fever persisted, however, especially in the evenings, up till the time of his discharge from hospital. The lungs appeared clear throughout. The urine contained much albumin at the beginning of the illness; this soon cleared up. There was no sign of a urinary infection. He became anæmic, the red cell count on the thirty-second day being 3,600,000 per cubic millimetre and the hæmoglobin value 67%. He slowly improved, sat out of bed on the fifty-fifth day, and was discharged from hospital on the sixty-second day. His convalescence was very prolonged. He was just about fit to resume work when, on December 31, an old corneal ulcer recurred, which further delayed him.

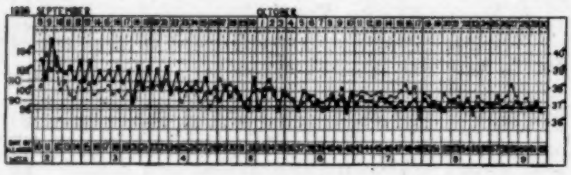

FIGURE V.
Chart of M.D. (Case VII). Continuous line = temperature; broken line = pulse rate.

Blood was injected into guinea-pigs on two occasions, that injected on the thirteenth day producing "Q" fever, that injected on the thirty-seventh day not producing "Q" fever. Urine was injected four times. The virus was obtained from the urine on the twenty-third and fifty-third days, but not on the thirteenth and seventy-ninth days.

This case was different in many respects from the others—in the severity of the illness, its prolonged duration and the development of jaundice. The diagnosis was very interesting. During the second week, when epistaxis occurred and jaundice developed, the condition seemed clinically to be a typical one of Weil's disease. The tests for leptospiræ, however, all gave negative results, and to our surprise the inoculated guinea-pigs developed "Q" fever.

Case VIII.

The notes of Case VIII are published by courtesy of Dr. K. S. McGregor.

L.T., aged thirty-three years, was admitted to Gympie Hospital on November 11, 1936, with a history of headache, pains all over, constipation, one attack of epistaxis and fever of four days' duration. There were a few spots on the abdomen suspicious of typhoid. The spleen was not palpable. The temperature ran an irregular course.

Blood was taken on November 12, and the clot was injected into a guinea-pig. The animal developed "Q" fever. The blood serum taken on November 20 did not agglutinate the usual test organisms.

Case IX.

The notes of Case IX are published by courtesy of Dr. G. E. B. Clayton.

J.H., aged fifty-five years, dairy farmer near Pomona, took to bed on November 10, 1936, with shivery attacks and very severe headache. There had been prodromal symptoms for the previous two days. On November 11 he was admitted to hospital. Next day there was a severe rigor. He had the typical typhoid facies for fourteen days. The headache was severe for four or five days, but not thereafter. There were scattered pains in the abdomen. There was a mild epistaxis once. There was no vomiting. The tongue was very furred in the early stages. The eyes were not injected, the spleen was not palpable, there was no rash of any kind, the stools showed nothing noteworthy.

The fever lasted for twenty-four days, terminating by a very gradual lysis. (See Figure VI.) The pulse rate remained practically normal while the fever was high. There was a faint cloud of albumin in the urine at the beginning. A sample of blood taken on the fourth day of illness gave "Q" fever to a guinea-pig. Another sample taken on the eleventh day was used for routine agglutination tests.

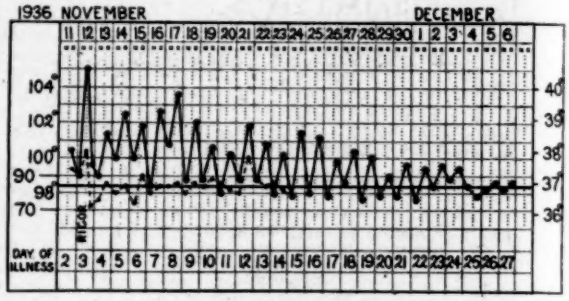

FIGURE VI.
Chart of J.H. (Case IX). Continuous line = temperature; broken line = pulse rate.

"Q" Fever in Guinea-Pigs.

Guinea-pigs are susceptible to infection with "Q" fever. They may be infected with blood or urine from human patients, or with blood or organ emulsion from infected laboratory animals. As so much of the present knowledge of the fever depends on guinea-pig experiment, it is necessary at this stage to describe the effects of "Q" fever in these animals. The description is based on the study of over 190 successful inoculations. The guinea-pigs used were mostly between 200 and 400 grammes in weight.

Incubation Period.

The incubation period varied from two to eighteen days. It tended to be longer when a smaller infecting dose was used. With ten guinea-pigs successfully inoculated with human material, that is, with a comparatively small dose of unadapted virus, the incubation period varied from eight to fourteen days with an average of 10·5 days. With much larger doses of adapted virus, as when guinea-pig liver was used for transmission, the incubation period might be as short as two days and was usually less than eight. (See Table IX.) The longest incubation periods were seen when minimal infecting doses were given, as in titration experiments. With these minimal doses the resulting infection might even be inapparent and an incubation period not ascertainable.

Signs and Symptoms.

The fever lasted usually about four to six days, sometimes for as short a period as one day, or for as many as eight. Its type was usually characteristic. (See Figure VII.) The fever typically began and ended abruptly. The temperature might reach 42° C., the average maximum of 50 cases being 40·9° C. Recurrence of the fever has not been observed.[1]

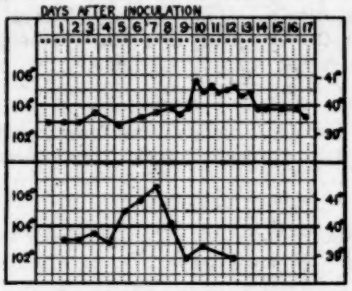

FIGURE VII.
Two temperature charts illustrating "Q" fever in guinea-pigs.

During the time of fever the guinea-pig became limp and lost appetite, and the hair stood out. There was rarely any obvious loss of weight, but there was as a rule for several weeks a failure of the normal increase in weight. The signs were not striking and the animal did not as a rule appear very ill. There was no pallor. The mortality was nil.

Very occasionally the infection in a guinea-pig was inapparent. The animal remained apparently well and afebrile. That infection had actually occurred was shown in one of two ways: (i) its blood or tissues about two weeks after inoculation transmitted the infection (Figure VIII), or (ii) it was found afterwards to be immune (Figure IX).

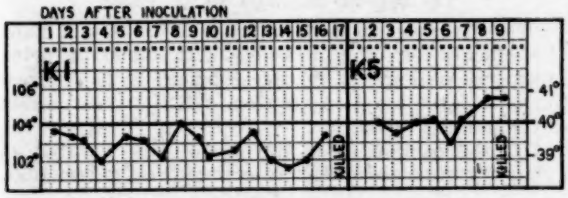

FIGURE VIII.
Inapparent infection with "Q" fever of guinea-pig *K*1 following injection of blood from E.K. (Case IV). Guinea-pig *K*5, injected with liver from *K*1, reacted typically.

Morbid Anatomy.

With animals killed during the fever, *post mortem* abnormalities were few. The spleen was always definitely enlarged. In the severe cases there were petechiæ in the wall of the caecum. Otherwise the organs showed no obvious abnormalities to the naked eye. Jaundice was never seen. There was no congestion or enlargement of the lymph glands. There was no sign of a scrotal reaction, nor was there, in guinea-pigs inoculated subcutaneously, any particular local reaction at the site of inoculation.

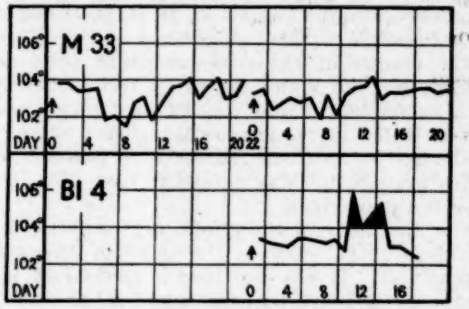

FIGURE IX.
Inapparent infection with "Q" fever of guinea-pig *M*33 following inoculation with a minimal dose of virus. When given a potent test dose of liver emulsion twenty-two days later, it proved immune. Control guinea-pig *BI* 4, given the same test dose, reacted well.

Immunity.

In the guinea-pig one attack of "Q" fever confers immunity.

This was first demonstrated in experiments with the *N* strain of "Q" fever virus, isolated from Patient I.

Three guinea-pigs were taken which at various times had been injected with this strain and had had a febrile attack. They were reinjected with it 24, 52 and 68 days respectively after the first injection. On these occasions each guinea-pig remained afebrile for twenty-one days, except for a reaction in two of them shortly after the injection. Control guinea-pigs injected at the same time ran the typical course of "Q" fever (Figure X).

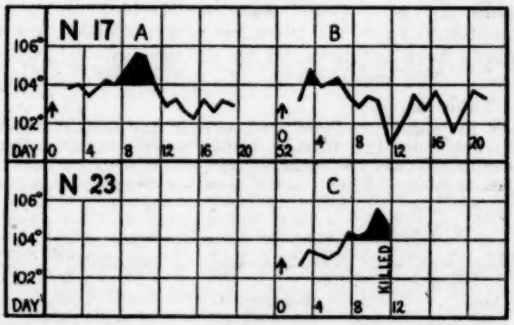

FIGURE X.
Immunity test. The temperature charts illustrate: *A*, an attack of "Q" fever in guinea-pig *N*17. *B*, immunity of *N*17 to a test inoculation 52 days later; the mild immediate reaction has no significance. *C*, definite reaction in control guinea-pig *N*23 to the same test dose.

Likewise four guinea-pigs, after being first infected with the *M* strain of the virus (isolated from Patient III), were found immune to a second injection of the same strain 23, 23, 27 and 30 days later.

It was next shown that there was a cross-immunity between the *N* and *M* strains. Three guinea-pigs, *N*4, *N*7 and *N*11 were first injected with *N* strain and tested by

[1] The temperature of normal guinea-pigs varies considerably. There may be a difference of one degree Centigrade or more between temperatures taken in the morning and afternoon, or before and after a meal. The temperature of our guinea-pigs was taken as a rule once a day, as far as possible in the afternoon. It is considered that under the conditions of these experiments an afternoon temperature is not abnormally raised unless it exceeds 40° C. Occasionally, on a specially hot and humid day, the temperature of a normal guinea-pig may somewhat exceed this.

injection with the *M* strain 88, 45 and 31 days later respectively. Two remained completely afebrile. One pig, *N*11, had a mild rise of temperature (to 40·3° C.) on one day only, the tenth. This was most likely without significance. Even if it was to be ascribed to a second attack of "Q" fever, it was a much milder attack than the control guinea-pig had—five days of fever, rising to 41° C., after an incubation period of six days. Guinea-pig *N*11 had a considerable, if not a complete, immunity.

Similarly, six guinea-pigs first infected with *M* strain were tested with the *N* strain 17, 24, 24, 24, 31 and 31 days later, and were all found immune.

The results of the cross-immunity tests demonstrated that the *N* and *M* strains were identical. As each subsequent strain was isolated in guinea-pigs, it was tested in the same way against one or more of the earlier strains. All the nine patients of this series were in this way proved to have been infected with the same virus.

The immunity of the guinea-pig conferred by one attack of "Q" fever is therefore of the greatest importance. It has provided a method of specific diagnosis for individual cases, and it has established "Q" fever as a pathological entity, thus confirming the opinion of physicians that it was a clinical entity. The use of the test in the diagnosis of human infections will be referred to again later.

The immunity lasts at least six months. Two guinea-pigs, tested after this interval, were found to be completely immune. Another guinea-pig was found immune after twelve months.

Treatment of Infected Guinea-Pigs.

Only one experiment in treatment has been made.

Seven guinea-pigs were taken, varying in weight between 300 and 350 grammes. They were all inoculated with "Q" fever. As soon as the temperature rose, four of them were each given an intramuscular injection of 0·003 gramme of sulpharsphenamine. The other three served as controls. There was no apparent improvement as the result of the treatment.

"Q" Fever in Other Laboratory Animals.

Rats.

Eleven rats caught wild in Brisbane have been inoculated with "Q" fever material. With three the effects were complicated by the presence of rat-bite fever. The results with the other eight are given in Table II.

Of the eight rats inoculated, at least five became infected, as shown by the further transmission of the infection to guinea-pigs. The transmission failed with the two rats that were not killed until three and four weeks after infection. The temperature reaction of the rats was insignificant, only two showing any rise, and then an evanescent one. The only abnormality to be found in the rats at *post mortem* examination was enlargement of the spleen in some of them.

Two unsuccessful attempts were made to raise the virulence of the virus for rats by a series of passages from rat to rat. In the first series the second passage rat failed to transmit the infection to the third. The second series was spoiled by the intrusion of rat-bite fever.

These experiments show that wild rats, both *Rattus norvegicus* and *Rattus rattus*, may be infected with "Q" fever, and that in them infection is usually of the inapparent form.

Mice.

Only a few experiments were made with mice. In view of Dr. Burnet's work these need not be detailed.

Rabbits.

Five rabbits have at different times been inoculated with "Q" fever virus.

One was injected with human blood, two with defibrinated guinea-pig blood, and two with guinea-pig liver. In every case the material used for injection was proved by guinea-pig inoculation to be virulent. There was no definite temperature reaction in any rabbit. Only one attempt was made to transmit the infection back from a rabbit to a guinea-pig. This was made with blood taken from Rabbit VI on the sixteenth day after inoculation. The inoculated guinea-pig was not infected.

Rabbit I was inoculated into the anterior chamber of the eye following the technique of Nagayo and his co-workers.[10] There was an immediate local reaction lasting about four days, but no later reaction as occurs with Japanese river fever virus. Descemet's membrane was not examined for Rickettsiæ, as the rabbit was preserved to see if it developed a Weil-Felix reaction.

The serum of each of the rabbits was tested with Proteus X19 and Proteus XK on various days after inoculation, as shown in Table III. In no case was any agglutination found. The tests were made with emulsions of living Proteus organisms, some with "H" and some with "O" cultures.

The Specific Diagnosis of "Q" Fever.

The diagnosis in each of the nine cases was made by inoculation of guinea-pigs with blood or urine from the patient, by the development of the characteristic fever reaction in them and by confirmation by immunity tests.

In the earlier cases the blood was citrated to simplify its subsequent injection into guinea-pigs.

TABLE II.

Experimental "Q" Fever in Rats.

Serial Number of Rat.	Species.[1]	Weight in Grammes.	Temperature Reaction.	Spleen.	Day After Infection on which Killed.	Rat Material Injected into Guinea-pig.	Result of Injection into Guinea-pig.
29	R.r.	145	None.	Small.	14	Liver	+
56	R.n.	125	None.	Very small.	22	Liver and kidney.	−
73	R.n.	270	None.			Blood 0·7 ml on thirteenth day.	−
				Rather large (1·75 grammes).	28	Liver and lung.	−
83	R.n.	235	None.	Small.	14	Liver and kidney.	+
89		102	None.	Rather large.	18	Liver and kidney.	+
96	R.n.	208	39° C. on fourth day. 39·2° C. on fifth day.	Rather large.	12	Liver and kidney.	+
108	R.r.	170	39·8° C. on fourth day.	Normal (0·84 gramme).	13	Liver and spleen.	+
97	R.n.	132	None.	Large (1·22 grammes).	15	Liver and spleen.	−

[1] R.n.—*Rattus norvegicus*; R.r.—*Rattus rattus*

TABLE III.
Weil-Felix Tests with Inoculated Rabbits.

Serial Number of Rabbit.	How Inoculated.	Weil-Felix Test.			
		Day After Inoculation.	Proteus X19.	Proteus XK.	Proteus X2.
1	Intraocularly with 0·15 mil of defibrinated guinea-pig blood, *N* strain.	19	–(H)	– (H)	– (H)
2	Intraperitoneally with 2 mils of defibrinated guinea-pig blood, *N* strain.	19 46	– (H) – (H, O)	– (H) – (H, O)	– (H)
4	Subcutaneously with 3 mils of citrated blood from Patient III, *M* strain.	12 60	– (H, O) – (H, O)	– (H) – (H, O)	
5	Intraperitoneally with 10 mils of guinea-pig liver emulsion, *M* strain.	40	– (H, O)	– (H, O)	
6	Intraperitoneally with 10 mils of guinea-pig liver emulsion, *K* strain.	14	– (O)	– (O)	

Later I preferred not to use the sodium citrate and to allow the blood to clot. The serum was drawn off and preserved, the clot was ground up and injected. There are good grounds for believing that when blood coagulates, the contained virus passes into the clot. By injecting the clot only, one avoids injecting as well any antibodies that may be present in the serum; and the serum is available for agglutination work. In most cases some of the clot was cultured in broth.

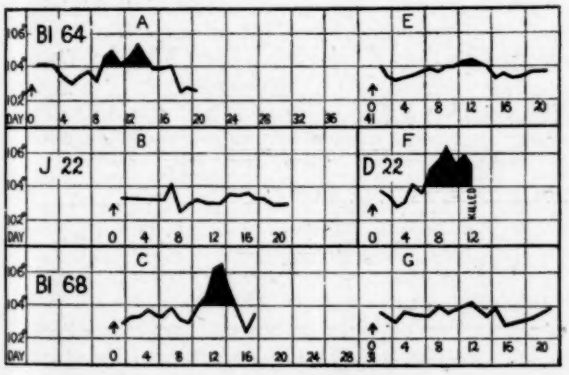

FIGURE XI.

Temperature charts of guinea-pigs illustrating the diagnosis of Case IX. *A*: Febrile reaction in guinea-pig *BI* 64 after injection of 1·5 mils of blood clot from the patient. *B*: No reaction in immune guinea-pig *J* 22, injected with 0·3 mil of blood from *BI* 64. *C*: Typical "Q" fever reaction in new guinea-pig *BI* 68, injected with 0·2 mil of blood from *BI* 64. Compare with curve *B*. *E*: No definite reaction in guinea-pig *BI* 64 to a test dose of the *D* strain of virus 41 days after the first injection. Compare with curve *F*. *F*: Characteristic "Q" fever response in guinea-pig *D* 22. It was injected with less than half the test dose given to *BI* 64. *G*: Complete immunity of guinea-pig *BI* 68 to a test dose of the *J* strain of virus. A control guinea-pig (not illustrated here) reacted typically.

When urine was used, it was injected as fresh as possible, in nearly every case within an hour of being passed. In the earlier cases 10 to 40 mils of urine were centrifuged and the deposit was injected, suspended in a small amount of urine. In the later cases 3 to 5 mils of urine were injected directly.

If the temperature of the injected guinea-pig rose, either it was killed and a liver emulsion was prepared, or blood was obtained from it by heart puncture. The liver emulsion or blood was then injected partly into a new guinea-pig and partly into one that had already had "Q" fever, and was therefore immune. If the new guinea-pig developed a typical fever and the immune one remained afebrile for three weeks, the diagnosis of "Q" fever was made. If the original guinea-pig was not killed during its fever, its immunity was tested after its recovery as a further check.

For example, 1·5 mils of blood clot from Patient IX were injected into guinea-pig *BI* 64 on November 17, 1936. The animal became febrile on November 26 and had six days of fever. (See Figure XI.) Blood was withdrawn from it on November 27, 0·2 mil being injected into a new pig, *BI* 68, and 0·3 mil into an immune pig, *J* 22. *BI* 68 had a typical fever reaction, *J* 22 had no rise in temperature. Finally, *BI* 64 and *BI* 68 were both tested and found immune, the former to *D* strain, the latter to *J*.

A shortened method of diagnosis is exemplified in the case of Patient V.

A sample of blood was taken from him into sodium citrate solution on the fifth day of the illness. One mil of the mixture (representing 0·8 mil of blood) was injected into a new guinea-pig *J* 1, and the same dose into guinea-pig *N* 39, immune by virtue of previous infection with the *N* virus. *J* 1 went through the characteristic course of "Q" fever; *N* 39's temperature remained normal, except for a slight reaction on the first day after injection. (See Figure XII.) In this case the diagnosis was made in fourteen days as against twenty-four with Case IX.

The shortened method is recommended if there is a moderate likelihood that the patient is suffering from "Q" fever, and if the blood is obtained early in the illness so that it contains abundant virus.

The Virus in Human Blood.

Table IV shows that the virus was found in the blood of the eight "Q" fever patients tested during the febrile period. Most of the tests were made with blood quite early in the illness while the temperature was high.

In Case IV the blood was taken on the last (ninth) day of fever. There could not have been much virus circulating then, or it was largely neutralized by antibodies, for the infection in the guinea-pig was inapparent and became obvious only on passage. Another specimen of blood taken from the same patient during convalescence failed to infect a guinea-pig. The blood of Patient VII was found infective on the thirteenth day of illness, but not on the thirty-seventh day when the temperature was approaching normal.

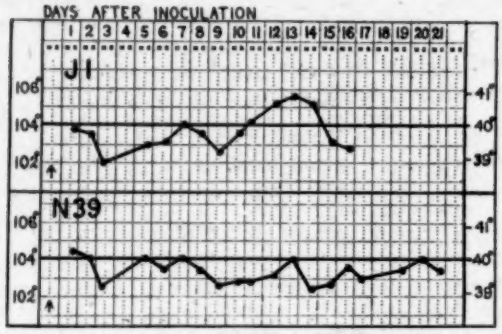

FIGURE XII.

Temperature charts of guinea-pigs *J1* and *N39*, illustrating the diagnosis of Case V. Each guinea-pig was injected with 0·8 mil of blood from the patient. *J1*, a new guinea-pig, reacted with four days' fever; *N39*, already immune to "Q" fever, remained afebrile.

It cannot be assumed from the almost uniformly successful results in these eight cases that inoculation of blood from patients with "Q" fever will always reproduce the fever in guinea-pigs. While this series was being collected, 23 other patients with fever of various kinds were investigated in this way. The negative results do not appear in this report, and one cannot say how many "Q" fever cases, if any, were represented among them. On the other hand, the blood of infected guinea-pigs, when 0·1 mil or more was injected, only failed once in 33 tests to transmit the infection, and on occasion much smaller doses succeeded. If an analogy can be drawn from the infectivity of guinea-pig's blood, it is likely that most human infections may be diagnosed by the inoculation of blood into guinea-pigs.

The last two patients lived some distance from Brisbane. With Case VIII there was an interval of two days between the taking of the blood and its injection into the guinea-pig. With Case IX, owing to the week-end intervening, there was an interval of four days. The samples were in the refrigerator for only a part of these times. Yet in each case the virus was still active.

This shows that it is practicable to send blood from a distant centre for "Q" fever diagnosis.

The Virus in Human Urine.

Table V shows the results of inoculating guinea-pigs with the urine of seven of the patients. It will be observed that the results with urine were much less consistent than with blood, the virus being obtained in only three of the seven. It is a noteworthy feature that the successful results with urine were obtained late in the illness or during convalescence. Patient II still had the virus in the urine after being afebrile for nineteen days and actually back at work.

Further Observations on the Guinea-Pig Immunity Test.

It has already been mentioned that a minimal dose of virus may give a latent infection. This occurred in Case IV. (See Figure VIII.) There

TABLE IV.

Results of Inoculation of Blood of "Q" Fever Patients into Guinea-pigs.

Case Number.	Date Blood Taken.	Day of Illness.	Date Blood Injected.	Amount of Blood Injected.	Result in Guinea-pig.	Remarks.
I	14/9/35	3	14/9/35	2·5 mils.	Probably positive.	
II						Not tested.
III	28/11/35	4	28/11/35	1·8 mils.	Positive.	Virus maintained through 11 passages.
IV	19/2/36 24/2/36	9 14	19/2/36 24/2/36	0·25 mil. 1·0 mil.	Positive. Negative.	Inapparent infection of first pig, obvious infection on passage. This sample of blood was taken during convalescence.
V	13/5/36	5	13/5/36	0·8 mil.	Positive.	Virus maintained through 30 passages.
VI	14/5/36	3	14/5/36	About 0·3 mil.	Positive.	
VII	11/9/36 5/10/36	13 37	11/9/36 5/10/36	Clot, 2·0 mils. Clot, 2·0 mils.	Positive. Negative.	Virus maintained through 5 passages.
VIII	12/11/36	6	14/11/36	Clot, 1·0 mil.	Positive.	
IX	13/11/36	4	17/11/36	Clot, 1·5 mils.	Positive.	

TABLE V.

Results of Inoculation of Urine of "Q" Fever Patients into Guinea-pigs.

Case Number.	Date Urine Obtained and Injected.	Day of Illness.	Day of Convalescence.	Amount Injected.	Result in Guinea-pig.	Remarks.
I	23/9/35	12		?	Positive.	Inapparent infection of first pig, obvious infection on passage.
	10/10/35	29	5	Deposit.	Positive.	Virus maintained through 16 passages.
II	17/9/35	11	2	Deposit.	Negative.	
	4/10/35	28	19	Deposit.	Positive.	
III	28/11/35	4		5·0 mils.	Negative.	
IV	24/2/36	14	5	Deposit.	Negative.	
	1/4/36	51	42	Deposit.	Negative.	
V	13/5/36	5		3·0 mils.	Negative.	
	19/5/36	11	3	3·0 mils.	Negative.	
	29/5/36	21	13	3·0 mils.	Negative.	
VI	19/5/36	8	2	3·0 mils.	Negative.	
VII	11/9/36	13		4·0 mils.	Negative.	
	21/9/36	23		4·0 mils.	Positive.	
	21/10/36	53		3·0 mils.	Positive.	Virus maintained through 9 passages.
	16/11/36	79	?	3·5 mils.	Negative.	
VIII						Not tested.
IX						Not tested.

was no apparent reaction in guinea-pig *K* 1, injected with the patient's blood. When *K* 1 was killed and passaged, the next pig, *K* 5, became obviously infected. If, therefore, the guinea-pig inoculated with human material remained apparently normal for fourteen days, it was then killed and an emulsion of the liver (perhaps with spleen and kidney also) was injected into a fresh guinea-pig. This procedure may be expected to detect an occasional case of "Q" fever that would otherwise be missed.

Occasionally in a test the immune guinea-pig has shown a slight reaction. This occurred in Case VII, and is illustrated in Figure XIII.

Injection of the patient's blood gave a febrile reaction in guinea-pig *D* 2. A liver-kidney emulsion of *D* 2 was injected into a new pig, *D* 5, which ran a typical fever curve beginning four days after injection, and into an immune pig, *J* 30. *J* 30 had two days of fever beginning fourteen days after injection.

It is possible that this had nothing to do with "Q" fever, for blood obtained by heart puncture on the second febrile day failed to infect another guinea-pig. In any case the reaction in the immune pig is not to be compared with the reaction in the new pig, *D* 5, and there can be no doubt about the reading of the result—*J* 30's previous infection with the *J* strain of virus had given it a considerable, if not a complete, immunity to the amount of *D* strain injected. The identity of the *J* and *D* viruses was fully confirmed by subsequent tests, in all of which the immunity to the test dose was complete.

If a new guinea-pig used in a test happened to be insusceptible to "Q" fever, the test would fail. A guinea-pig insusceptible in the terms of the dosage

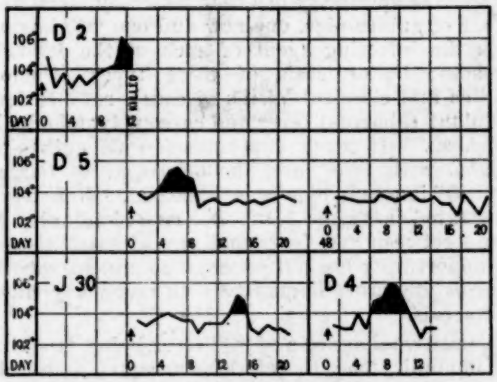

FIGURE XIII.

Temperature charts of guinea-pigs illustrating the diagnosis of Case VII. Guinea-pig *D*2, injected with two mils of blood clot from the patient, reacted with fever. Guinea-pig *D*5, injected with a liver-kidney emulsion from *D*2, reacted strongly and rapidly; it proved immune to a test injection of the *J* strain of virus 48 days later. Immune guinea-pig *J*30, injected in the same way from *D*2, showed only a mild delayed reaction of doubtful significance. Control guinea-pig *D*4 showed a vigorous "Q" fever reaction, although it was injected with only a tenth of the test dose given to *D*5.

used in this work must be a rarity, if indeed it exists. In the long series of inoculations, no new guinea-pig has failed to react when inoculated with

guinea-pig liver obtained during the period of fever. One guinea-pig, already referred to, inoculated with guinea-pig blood unexpectedly failed to become infected. There may have been some reason other than insusceptibility to explain this result. However, in view of this failure, and the occasional cases in which immunity to the test dose appeared to be partial only (immunity being always relative), and the possibility of a raised temperature in a test animal being due to a concurrent infection, it has been thought advisable not to depend in any experiment upon the results with one pair of guinea-pigs only.

During this investigation the blood of twenty-three febrile patients, other than the nine of this series and one with leptospirosis, was inoculated into guinea-pigs. Most of the guinea-pigs did not react at all; a few showed fever of indefinite type, which either could not be reproduced in passage or which did not make the guinea-pig immune to "Q" fever. The illnesses of some of these twenty-three patients were afterwards diagnosed definitely as typhoid fever, septicæmia, pneumonia and tuberculosis. In no case in which a diagnosis of one of these diseases was established did the corresponding guinea-pig react in the way characteristic of "Q" fever.

There are, however, many infections to which guinea-pigs are susceptible. A febrile reaction by itself would not be sufficient to sustain a diagnosis of "Q" fever, although a fever of characteristic type would be strongly suggestive. It is necessary to test further in a "Q"-immune guinea-pig any infection obtained.

The immunity given to a guinea-pig by an attack of "Q" fever is specific as far as it has been investigated. The specificity has been tested by inoculating a pair of guinea-pigs, one new and one "Q"-immune, with the infecting agent of each of the following diseases: leptospirosis of three types (Pomona, Ballico and classical Weil's disease), rat-bite fever, undulant (abortus) fever and caseous lymphadenitis of sheep. In each experiment both guinea-pigs reacted with fever, and the behaviour of the new and "Q"-immune pigs was identical. One test is illustrated in Figure XIV. No cross immunity was found between "Q" fever and any of these diseases. An opportunity has not yet come to find out whether there is any cross immunity with murine typhus or psittacosis.

A positive diagnosis of "Q" fever based on guinea-pig immunity may therefore be accepted as reliable. A negative result would not exclude "Q" fever. It should be added that in most of the nine cases diagnosed as "Q" fever in this way, no alternate diagnosis was possible. Culture of the blood and tests for agglutination with the organisms of the common fevers all gave negative results (Table VI).

The guinea-pig immunity test has been of great value in detecting these nine cases, in studying the disease and in establishing "Q" fever as an entity. However, the long time that it takes—two to four weeks—greatly limits its clinical value.

The Clinical Differential Diagnosis.

A satisfactory discussion of this subject must await fuller knowledge and be based on the clinical study of a larger series of cases. At this stage, however, a reference will be made to points that may assist in the making of a clinical diagnosis early in the illness.

The possibility of "Q" fever is to be borne in mind in the presence of a high fever of acute onset, accompanied by a severe headache, a comparatively slow pulse rate, and no other obvious localizing symptoms.

The other fevers to be considered are influenza, the typhoid-paratyphoid group, typhus and the leptospiroses.

"Q" fever is to be distinguished from influenza by the mildness or absence in the former of localized respiratory symptoms (coryza, sore throat, cough), by the comparatively slow pulse rate, and by the sporadic distribution. Nevertheless in some of the cases of "Q" fever mild respiratory symptoms were present, and these patients were naturally regarded as suffering from influenza until the continuance of the fever excluded it. If cases of "Q" fever should occur with a very short course, they would be hard to distinguish from influenza.

From typhoid and paratyphoid fevers, "Q" fever may perhaps be distinguished by its more acute onset and the absence of diarrhœa. But the clinical state of the patient with "Q" fever may appear very similar to that of a typhoid patient. Later in the illness the failure of the specific tests and, if it occurs, an abrupt defervescence will exclude the typhoid group.

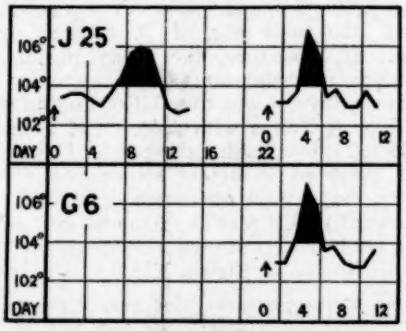

FIGURE XIV.

Temperature charts of guinea-pigs, showing the absence of cross immunity between "Q" fever and leptospirosis of the Pomona type. Guinea-pig *J25* was first given "Q" fever, to which it reacted typically. Twenty-two days later it was given leptospirosis, to which it reacted just as well as the control guinea-pig *G6*, which had never had "Q" fever.

The absence of a distinctive rash in the first week of a fever will speak strongly against typhus, and the absence of a Weil-Felix reaction in the second week will practically exclude it. The distribution of cases and the nature of onset are rather similar in "Q" fever and urban typhus.

In one case (Case VII), in which jaundice was present, there was a close resemblance clinically to Weil's disease, the final diagnosis of "Q" fever

TABLE VI

Results of Blood Culture and Serum Agglutination Tests.

Case Number.	Day of Illness.	Blood Culture.	Serum Agglutination Tests									
			Eberthella typhosa.	*Salmonella paratyphi.*	*Salmonella schottmülleri.*	*Salmonella hirschfeldii.*	Proteus X19.	Proteus XK.	Proteus X2	Proteus XL.	*Brucella abortus.*	*Pseudomonas aeruginosa*
I	7	–	–	–	–		– (H)	– (H)			–	–
	14	–	–	–	–	–	– (H)	– (H)			–	–
	29		–	–	–		– (H)	– (H)			–	–
II	11		–	–	–		– (H)	– (H)			–	–
III	4	–										
	22		–	–	–	–	– (H, O)	– (H, O)			–	–
IV	14						– (H, O)	– (H, O)	– (H)			
V	5	–										
	132		–	–	–	–	– (O)	– (O)			–	
VI												
VII	11	–[1]	–[1]	–[1]	–[1]							
	23		–	–	–	–	– (O)	– (O)			–	
	33		–[1]	–[1]	–[1]							
	37						– (O)[2]	– (O)[2]	– (O)[2]	– (O)[2]		
VIII	14		–	–	–		– (O)	– (O)			–	
IX	11		–	–	–		– (O)	– (O)			–	

– means that the result of the test was negative.
[1] These tests were done in the laboratory of the Brisbane General Hospital. (Dr. G. C. Taylor, Acting Pathologist.)
[2] These tests were done by Dr. R. Y. Mathew, Commonwealth Health Laboratory, Cairns.
The Weil-Felix tests were at first done with motile (H) cultures, later with non-motile living (O) cultures.

depending on the pathological tests. Of the non-icteric leptospiroses the form most likely to be encountered in south Queensland is seven-day fever. Congestion of the conjunctivæ at the onset, shorter duration of the fever, and a special incidence in summer and autumn would strongly suggest this diagnosis.

The Virus of "Q" Fever.

Strains.

The first strain of the virus to become established in the laboratory was the *N* strain obtained from the urine of Patient I. It was maintained through sixteen passages in guinea-pigs. The next strain, *M*, from the blood of Patient III, was maintained for eleven passages. The earlier studies were made with these two strains. For economy of guinea-pigs, passage of the *N* strain was stopped. Shortly afterwards the *M* strain was lost through storing too long the liver emulsion containing it.

The *J* strain, from the blood of Patient V, has been maintained by passage in guinea-pigs ever since it was obtained in May, 1936. It has now (April, 1937) undergone thirty passages. Most of the later work on the virus has been done with this strain. It does not appear to have altered in virulence or in any other way while under observation.

The first *D* strain was obtained from the blood of Patient VII. An emulsion of the liver of the third-passage guinea-pig (*D*6) was sent in ice to Dr. F. M. Burnet in October, 1936. The strain kept in Brisbane unfortunately died out after five passages. The fifth-passage pig (*D*11) ran the typical course of "Q" fever. On the second day of fever 0·6 mil of blood was taken from it and injected intraperitoneally into guinea-pig *D*15. *D*15 unexpectedly failed to react, and the series terminated. This is the example already mentioned of failure of transmission with blood. Another *D* strain from the same patient's urine went through ten passages and its transmission was then discontinued.

The strains from the other patients were kept going only long enough to establish their identity with the stock strains.

For the future it has been decided to maintain one strain only of the "Q" fever virus—the *J* strain.

Attempts to Cultivate and Detect the Infecting Agent.

The blood of four of the patients was cultured in various media without success. The blood and spleen of infected guinea-pigs were repeatedly inoculated into a variety of media and incubated aerobically, anaerobically and in an atmosphere with 10% carbon dioxide. Quite a number of organisms have grown on these media, but all have proved harmless when reinjected into guinea-pigs. The infecting agent of "Q" fever has not been cultivated.

Smears of blood and organs of infected guinea-pigs have been stained in various ways, but no significant microorganism has yet been seen in them. Nor has one been recognized by dark-ground examination. This work was done on guinea-pig tissues only. Reference may here be made to Dr. Burnet's success in finding rickettsial bodies in the spleens of infected mice.

Resistance of the Virus.

The virus contained in a liver emulsion may maintain its infectivity for several months if kept in the refrigerator at a temperature of about 5° C. Table VII shows the results of a number of observations on this point. It will be seen that the emulsion prepared from the liver of guinea-pig *M*9 was still potent after three months of storage, but was inert after four months. The *M*38 emulsion infected a guinea-pig after 47 days, but not after 64. Three other emulsions lasted at least 20 to 28 days.

No doubt the loss of potency with storage is a gradual one. Quantitative experiments to investigate this have not been done, but a gradual loss of potency of the *M*38 emulsion is hinted at by the increase in the incubation period of the test animals concurrently with the length of storage.

It was too hastily assumed that, because the *M*9 emulsion lasted three months, other emulsions would do the same. Passage of the *M* strain in guinea-pigs was therefore suspended during a rush of other work, and the *M*38 emulsion was stored, in the expectation of resuming the series of passages later. But when this was attempted after 64 days the emulsion was inert, and the *M* strain was lost.

In spite of this unfortunate occurrence the fact that the virus may be preserved in the refrigerator for a month or more has been of great help in the work. For instance, when the *M* strain was lost, recourse was had to a stored liver emulsion from guinea-pig *J*1. This was apparently unimpaired by a storage of twenty-eight days, and a new series of passages was begun. Frequently material has been stored for a few days to suit the convenience of the work.

One experiment only has been made to test the resistance of the virus to glycerol. An infective liver emulsion was mixed with an equal part of glycerol and stored at 5° C. After twenty-one days it was still infective.

The Distribution of Virus in the Tissues.

It has already been seen that the virus may be found in the blood of human patients during the fever, and less commonly in the urine late in the illness or during convalescence.

With infected guinea-pigs also the virus is present in the blood during the fever. On 32 out of 33 occasions in which at least 0·1 mil of such blood was inoculated into new guinea-pigs, the infection was transmitted.

The liver of a guinea-pig is an even more potent source of the virus than the blood. Liver emulsions were prepared by crushing the liver in a mortar or a Griffith's tube with about five to ten times its volume of saline solution and lightly centrifuging to remove the larger particles. In quantitative work the piece of liver was weighed and then ground thoroughly with sand. Emulsion of infected liver

TABLE VII.

Preservation of the Virus by Storage at 5° C.

Material Injected.	Dose.	Time Stored at 5° C. (Days.)	Guinea-pig Injected.	Result.[1]	Incubation Period. (Days.)	Duration of Fever. (Days.)
Liver emulsion *M*9	0·1 mil.	0	*M*22	+	10	2
		32	*BI* 2	+	10	3
		59	*M*44	+	10	4
		92	*M*45	+	12	6
		123	*M*51	−		0
Liver emulsion *M*38	0·5 mil.	6	*M*38	+	6	4
		6	*M*39	+	6	4
		37	*N*40	+	8	4
		37	*M*46	+	8	4
		37	*M*47	+	8	6
		47	*M*49	+	12	6
		64	*M*50	−		0
		85	*M*52	−		0
Liver emulsion *N*36	0·2 mil.	0	*N*29	+	12	4
		20	*M*34	+	11	6
		20	*BI* 4	+	11	4
		20	*BI* 6	+	12	5
Liver emulsion *J*1	2·8 mils.	28	*J*9	+	9	At least 3
Liver emulsion *K*8 and *K*9 mixed.	0·5 mil.	24	*K*11	+	11	At least 3
		24	*K*13	+	11	5
		81	*BI* 24	−		0
		81	*BI* 28	−		0
		81	*J*4	−		0

[1] + means that the guinea-pig became infected; − means that it did not.

TABLE VIII.
Titration of Virus in Blood and Liver of Guinea-pigs.

Donor Guinea-pig.	Material Injected.	Dose.	Recipient Guinea-pig.					Result.
			Number.	Incubation Period. (Days.)	Duration of Fever. (Days.)	Maximum Temperature. (°C.)	Subsequent Immunity.	
*M*10, killed on second day of fever	Whole blood	2·5 mils.	*M*12	9	3	40·9	Immune.	+
		0·1 mil.	*M*13	9	5	40·9	Not tested.	+
		0·01 mil.	*M*14	10	At least 5	41·3	Killed and passaged.	+
		0·001 mil.	*M*15	11	1	40·2	Not tested.	+
	Liver	0·5 gramme.	*M*16	6	At least 1	40·9	Killed and passaged.	+
		0·03 gramme.	*M*17	9	4	41·2	Immune.	+
		0·003 gramme.	*M*18	8	At least 3	41·7	Killed and passaged.	+
		0·0003 gramme.	*M*19	13	4	40·7	Immune.	+
*J*9, killed on third day of fever	Blood plasma	0·01 mil.	*J*10	9	6	41·7	Not tested.	+
		0·001 mil.	*J*11		0		Not immune.	−
		0·0001 mil.	*J*12		0		Not immune.	−
		0·00001 mil.	*J*13		0		Not tested.	−
	Liver	0·1 gramme.	*J*4	4	7	40·9	Not tested.	+
		0·01 gramme.	*J*8[1]	8	2	41·2	Not tested.	+
		0·001 gramme.	*J*18	7	5	41·2	Not tested.	+
		0·0001 gramme.	*J*19	7	5	41·3	Not tested.	+
		0·00001 gramme.	*J*20	8	6	41·0	Immune.	+

[1] Guinea-pig *J*8, 475 grammes, was much larger than the other guinea-pigs.

in a dose of at least 0·1 mil was injected at various times into 75 new guinea-pigs. All became infected, though in one case the infection was latent only.

A complete quantitative estimation of the relative concentration of virus in the different organs has been out of the question because of the large number of guinea-pigs that would be required. Titrations of blood and liver have been made twice, and the results are shown in Table VIII.

The table indicates that as the infecting dose became smaller, the incubation period as a rule became longer. With the *M*10 material the incubation periods show that the minimum infective doses of both blood and liver were almost reached with the highest dilutions. With the liver of *J*9, however, it would appear that still smaller doses might have been successfully given. The first liver contained at least 3,000, the second at least 100,000 minimum infecting doses per gramme.

That the virus is more concentrated in the liver than in the blood is confirmed by the shorter incubation period on the average in guinea-pigs infected with liver (Tables VIII and IX).

TABLE IX.
Comparative Incubation Periods in Guinea-pigs Infected with Blood and Liver.

Injection Material.	Dose.	Number of Cases.	Incubation Period (Days).		
			Shortest.	Longest.	Average.
Blood.	0·5 mil or more.	9	5	9	7·1
	0·1 to 0·4 mil.	19	5	13	9·4
	Total: 0·1 mil or more.	28	5	13	8·6
Liver emulsion.	0·5 mil or more.	46	2	8	5·4
	0·1 to 0·4 mil.	28	3	11	6·5
	Total: 0·1 mil or more.	74	2	11	5·8

One mil of liver emulsion would represent roughly 0·1 gramme of liver.

Blood and liver may already be infective in the latter part of the incubation period.

For instance, guinea-pig *N*19 was killed on the ninth day after injection, before there was any rise of temperature. Two mils of its blood infected guinea-pig *N*20. Guinea-pig *J*26 was accidentally killed eight days after inoculation and before any reaction occurred. An emulsion of its liver infected *J*27.

The infectivity of guinea-pig blood and liver may persist for at least seven days after the fever is over. Some observations on this point are given in Table X.

The persistence of the virus allows the full course of the fever to be observed in a test guinea-pig and the same animal then to be used for passage. No doubt the amount of virus is rapidly decreasing during this time. The long incubation periods in the successful cases in Table X show that only a small amount was present a week after the fever was over.

Only four attempts have been made to find the virus in guinea-pig urine. In two the urine was taken during the fever, in the others during convalescence. All the attempts failed.

Epidemiology.

Despite considerable work, much about the epidemiological aspect of "Q" fever remains obscure. Some information of epidemiological interest is given in Table XI.

No predilection for any particular season of the year is apparent, either in the present series of nine cases or in a previous series of twenty probable but unproved cases.

Six of the patients were domiciled in Brisbane, another one near by. There was one patient each from Pomona and Gympie, 86 and 106 miles respectively north of Brisbane. "Q" fever appears likely, therefore, to have a wide distribution in the south of Queensland.

Table X.

Infectivity of Guinea-pig Tissues in Convalescence.

Donor Guinea-pig.	Day of Convalescence.	Material.	Dose.	Recipient Guinea-pig.					Result.
				Number.	Incubation Period. (Days.)	Duration of Fever. (Days.)	Maximum Temperature. (°C.)	Subsequent Immunity.	
J57	3	Blood.	0·2 mil.	J66		0		Not immune.	−
M24	7	Blood.	0·6 mil.	M29	13	1	40·4	Immune.	+
N29	7	Blood.	2·25 mil.	N39	13	8	41·1	Immune.	+
	7	Urine.	0·65 mil.	N40		0		Not immune.	−
	7	Liver emulsion.	1·5 mils.	N41	10	6	41·3	Not tested.	+
N26	10	Blood.	0·4 mil.	B1 6		0		Not immune.	−
	10	Urine.	0·6 mil.	B1 4		0		Not immune.	−
M10	32	Liver emulsion.	1·0 mil.	B7		0		Not immune.	−

Table XI.

"Q" Fever Patients. Epidemiological Information.

Number of Patient.	Age.	Date of Onset.	Domicile.	Occupation.
I	50	September 12, 1935.	Brisbane.	Worker among hides.
II	29	September 7, 1935.	Brisbane.	Meat inspector.
III	45	November 25, 1935.	Near Brisbane.	Dairy worker.
IV	18	February 11, 1936.	Brisbane.	Worker on beef slaughter floor. He swept the floor and picked up scraps.
V	17	May 9, 1936.	Brisbane.	Worker with beef gut.
VI	37	May 12, 1936	Brisbane.	Mutton slaughterman.
VII	36	August 30, 1936.	Brisbane.	Braceman on new sewerage excavation.
VIII	33	November 7, 1936.	Gympie.	Labourer on dairy farm.
IX	55	November 10, 1936.	Pomona.	Dairy farmer.

All the patients were men. Five were meat workers and three dairy farmers. It is impossible at present to state what relation, if any, "Q" fever has to occupation. Patient I had been working at the abattoir off and on for twenty years, and continuously for the seven years before his illness. On the other hand, Patient V had been working there for only six weeks when he became ill.

An intriguing point is the falling ill of two or three abattoir workers at the same time. The first two patients in this series became ill within a few days of one another. A third abattoir worker, a stockman, also sickened at the same time with an illness resembling "Q" fever clinically, but not proved pathologically. Not one of the three met either of the others in the course of his work, nor could any significant common factor be discovered. Patients V and VI also fell ill within a few days of each other, and there were two other instances of the same phenomenon in the series of twenty probable cases. In no instance was there any obvious relation between the men simultaneously attacked.

Possible Modes of Infection.

Guinea-pigs are easily infected by injection, either subcutaneous or intraperitoneal. A few attempts have been made to infect them in other ways, but without any obvious success. The results are given in Table XII.

Three out of four guinea-pigs that ate infected liver failed to become infected; in the other the infection was inapparent only. One of the four had a febrile reaction after eating, not due to "Q" fever, for on being tested it was found not immune. As the amounts of liver eaten without ill-effect by these guinea-pigs must have contained thousands of minimal infective doses, ingestion can hardly be the method of natural spread of "Q" fever.

The abundance of the virus of "Q" fever in the blood and the ease with which the disease may be transmitted by injection render it likely that some blood-sucking vector is responsible for the natural transmission and that there is a reservoir of infection in some animal.

The laboratory stock of guinea-pigs carry the common guinea-pig lice, *Gyropus ovalis* and *Gliricola porcelli*. Twenty lice were taken from a guinea-pig on the fourth day of its attack of "Q" fever and injected into another guinea-pig. The infection was not transferred. This result was not unexpected, seeing that these are biting lice and not blood-suckers, and that new guinea-pigs do not get "Q" fever when kept in the same jar as infected pigs.

Search for an Animal Reservoir of Infection.

The fact that minute doses of blood or liver can infect a guinea-pig has allowed the mass testing of animals. Equal amounts of blood or liver were

TABLE XII.

Experiments in Transmission by Various Routes.

Attempted Method of Transmission.	Material Used.	Amount.	Recipient Guinea-pig.				Result.
			Number.	Incubation Period. (Days.)	Duration of Fever. (Days.)	Subsequent Immunity.	
Ingestion	Liver, *M*16.	2·0 grammes.	*M*21	–	0	Immune.	Inapparent infection.
	Liver, *J*57	2·0 grammes.	*J*65	–	0	Not immune.	–
	Liver, *J*78.	4·5 grammes.	*J*80	–	1 (?)	Not immune.	–
			*J*81	7	4	Not immune.	–
Application to lightly scratched skin	Blood, *J*73.	One drop.	*J*76	–	0	Doubtful.	Doubtful.
	Liver emulsion, *J*73.	One drop.	*J*77	–	0	Not immune.	–
Rubbing on intact skin	Liver, *M*18.		*M*22	–	0	Not immune.	–
Instillation into conjunctival sac	Liver emulsion, *N*25.	One drop.	*N*22	–	0	Doubtful.	Doubtful.
	Liver emulsion, *J*57.	One drop.	*J*63.	–	0	Not immune.	–
Contact			*M*9[1]	–	0	Not immune.	–
			*J*49[2]	–	1 (?)	Not immune.	–
			*J*51[2]	–	1 (?)	Not immune.	–
Injection of guinea-pig lice	20 lice, collected from *J*73 on fourth day of fever, ground up and injected.		*J*75	–	1 (?)	Not immune.	–

[1] Kept with a succession of infected guinea-pigs for 30 days.

[2] Kept with a pair of febrile, then convalescent, guinea-pigs for seven weeks.

collected from a series of animals at the time of slaughter and mixed together. Small portions of the mixture were then injected into guinea-pigs. The results of this work are given in Table XIII.

The results with the bullocks and sheep were entirely negative so far as they went.

The investigation of the pigs was rendered difficult by contamination of the samples at the time of collection.

Three of the eight guinea-pigs injected with pig material promptly died; four others developed local infections with an irregular fever, which obscured any possible "Q" fever reaction. To try to overcome the contamination an equal part of glycerol was added to one sample of mixed liver emulsion some days before injection. The complicating infection was reduced, but sloughing occurred.

Two of the guinea-pigs injected with pig's blood gave a doubtful result in the subsequent immunity test, but no strain of "Q" fever virus was obtained in passage from the test guinea-pigs that were killed.

A series of 72 wild rats caught in Brisbane was also examined for "Q" fever. The species were *Rattus norvegicus* (50) and *Rattus rattus* (16). The species of the other six was not recorded. Twenty-four guinea-pigs were injected with liver (usually kidney and brain also) from 69 rats, in batches of one to seven at a time; one guinea-pig was injected with blood from the other three rats. Four of the guinea-pigs died of general peritonitis. Most of the others were killed on the fourteenth day, and their liver was reinjected into other guinea-pigs. In no case was the virus of "Q" fever obtained from the rats.

TABLE XIII.

Mass Testing of Animals for "Q" Fever.

Animal.	Number of Animals in a Batch.	Material.	Guinea-pig.	Result.	Remarks.
Bullocks	100	Citrated blood	*BI* 1	–	Not immune after.
			BI 2	–	Not immune after.
	83	Liver	*BI* 16	–	Killed, another guinea-pig injected.
			BI 17	–	Not immune after.
Sheep	102	Citrated blood	*BI* 6	–	Not immune after.
	100	Liver	*BI* 12	–	Not immune after.
			BI 13	–	Developed caseous lymphadenitis.
Pigs	64	Citrated blood	*BI* 3	–	Died the same day.
			BI 5	Doubtful.	Ran irregular fever. Subsequent immunity test doubtful.
	32	Citrated blood	*BI* 9	–	Killed, another guinea-pig injected.
			BI 10	Doubtful.	Ran irregular fever. Subsequent immunity test doubtful.
	16	Citrated blood	*BI* 11	–	Not immune after
	78	Liver	*BI* 14	–	Died from general peritonitis.
			BI 15	–	Died from general peritonitis.
		Glycerolated liver	*BI* 24	–	Killed, another guinea-pig injected.

"Q" Fever and the Typhus Group.

"Q" fever as here described does not correspond with any fever of which I am aware. The nearest relationships are with psittacosis and the typhus group. To typhus it has been necessary to make frequent reference in the text. It is convenient now to summarize the resemblances and divergences between "Q" fever and the typhus group.

The course of the fever in some of the "Q" fever cases—continuously high, then rapidly falling early in the second week (Figures II and IV)—is rather similar to the course of urban typhus. The longer type of "Q" fever terminating by lysis (Figures III and VI) may be paralleled by occasional cases of the rural typhus of Malaya[3] and elsewhere, although Malayan typhus, like the *K* typhus of north Queensland, usually terminates within seventeen days.

The febrile and immunological responses of guinea-pigs to "Q" fever have a general resemblance to their responses to the typhus viruses. The literature of experimental typhus research has been of great assistance to me in this guinea-pig work. The immunity experiments here described are similar to those performed, for instance, at the Institute for Medical Research, Kuala Lumpur, on tropical typhus, and described in the "Annual Reports" and other publications. And the method of setting out the results of the immunity tests (Figures IX, X, XI, XIII and XIV) I have copied from an article by Pijper and Dau on the typhus-like fevers of South Africa.[4] It has not yet been possible to test for any cross immunity between "Q" fever and fevers of the typhus group.

On the other hand, there are important differences in the guinea-pig reactions. For example, "Q" fever differs from rural typhus in the much greater susceptibility of the guinea-pig to the former, and it differs from urban or murine typhus in the absence of the characteristic scrotal reaction.

Dr. Burnet's discovery of a rickettsial organism as the cause of "Q" fever provides another resemblance to the typhus group.

Because of these resemblances, a Weil-Felix reaction has been carefully looked for with "Q" fever. But no reaction could be obtained, either in the human cases (Table VI) or in rabbits inoculated with three strains of "Q" virus (Table III). In view of the importance of the point, I took advantage of Dr. R. Y. Mathew's large experience with the test at the Commonwealth Health Laboratory, Cairns. He kindly tested the serum of Patient VII (thirty-seventh day) and found no agglutination with the OX19, OXK, OX2 or OXL strains of Proteus.

Another important divergence from the typhus group is the absence of a characteristic rash with "Q" fever. Only one of the nine patients had an obvious rash, and that was a late one, on the fourteenth day. On the other hand, a rash is a striking and characteristic feature of typhus and commonly appears before the end of the first week. Though many patients may run their course without one, a series of typhus cases could hardly fail to include a fair proportion with a rash.

The typhus group of fevers includes many individual varieties. Among them there is considerable diversity in the details of the clinical course, the rash, the degree of guinea-pig susceptibility and the Weil-Felix reaction. "Q" fever does not appear to correspond with any of the known varieties. It is certainly quite distinct from the two types endemic in Queensland—the urban or murine typhus of the cities and the rural or *K* typhus of the northern scrubs. In this section comparison of "Q" fever has advisedly been made with the generality of the group. There are some suggestive resemblances, but the divergences are important. The exact relationship, if any, between "Q" fever and the typhus group remains for the future to decide.

Summary.

There occurs in Queensland a fever entity of a type not previously differentiated. It has provisionally been named "Q" fever, and nine cases are here described.

"Q" fever does not appear to correspond with any known fever. It has certain resemblances to the typhus group, but is distinguished therefrom in various ways, particularly by the absence of a characteristic rash and by the consistently negative response to the Weil-Felix test.

The onset of the illness is acute. The course and duration of the fever vary. In some cases there is a rapid defervescence after about six to nine days; in others the course is protracted to the third or four week or more and the fall of temperature is gradual.

The outstanding symptom is headache. It may be severe and persistent and is in most cases the chief complaint. The pulse rate is comparatively slow.

None of the cases has been fatal.

Guinea-pigs are susceptible to "Q" fever, and they were infected by inoculation of blood or urine from each of the nine patients. Infected guinea-pigs show as a rule a characteristic fever of about four to six days' duration. Mild infections may be inapparent. The mortality in guinea-pigs is nil. If the guinea-pig is killed during the fever, the spleen is found to be enlarged.

One attack in a guinea-pig confers immunity. The immunity, being specific, has provided a means for the specific diagnosis of "Q" fever. In this way it has been proved that the infecting agent was the same in each of the nine cases, and therefore that "Q" fever is a definite pathological entity. Its existence as a clinical entity had previously been suspected.

Rats are mildly susceptible to "Q" fever and develop the disease in an inapparent form. Rabbits are insusceptible.

The infecting agent of "Q" fever is present in the blood of human patients during the fever period. It may also be present in the urine in the later stages of the illness and in convalescence. It is also present

in the blood and particularly the liver of infected guinea-pigs. Minute amounts of these will transmit the infection to other guinea-pigs.

The *J* strain of "Q" fever virus has been maintained in the laboratory for nearly a year by passage from guinea-pig to guinea-pig. It has undergone thirty passages. Other strains were maintained for sixteen and eleven passages.

The virus has not been cultivated on artificial media, nor has it yet been seen by microscopic examination of human or guinea-pig tissues.

When material containing the virus is stored in the refrigerator, it retains its virulence for a month or more.

The epidemiology of "Q" fever is obscure. There is no obvious relation to the season. Most of the cases occurred in meat workers or dairy farmers. It is suspected that there may be a reservoir of infection in some animal with a blood-sucking parasite as a vector. Attempts to find such a reservoir have so far failed.

The fevers of the Queensland coast have long provided a complex problem. For many years the composite nature of "coastal fever" has been evident, and recent years have witnessed the culling out from the chaos, one by one, of a number of definite entities. "Q" fever is now the latest to be differentiated; it is not likely to be the last.

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EXPERIMENTAL STUDIES ON THE VIRUS OF "Q" FEVER.

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THE experiments to be described have been carried out with infective material originally derived from a saline emulsion of guinea-pig liver, "D.6", received from Dr. E. H. Derrick. We had no difficulty in reproducing in guinea-pigs with this material the characteristic febrile reaction described by Derrick in the preceding paper. The virus has been maintained by guinea-pig passage without significant change in the type of reaction for about twenty passages. We have found no characteristic macroscopic or microscopic changes in the organs of infected guinea-pigs. Attempts to cultivate bacteria or leptospira gave negative results, and appropriate microscopic examinations for leptospira and for Rickettsiæ (in smears from the tunica) were equally without result.

On the provisional hypothesis that a filtrable virus was responsible for the febrile reaction in guinea-pigs, a series of studies was made along the orthodox lines of virus research to determine the characteristics and range of pathogenicity of the virus responsible.

Pathogenicity of the Virus for Laboratory Animals.

Guinea-Pig.—The guinea-pig reactions have been described by Derrick and will not be discussed here. Temperature charts of control animals included in certain active immunity experiments are shown in Figure V. As might be expected, our normal temperature level for guinea-pigs is about a degree lower than in Brisbane, and we have adopted 39·4° C. (103° F.) as the upper normal limit of temperature.

Monkey.—A monkey (*Macacus rhesus*), M.1, was inoculated with infected guinea-pig liver emulsion.

Three intradermal inoculations of 0·1 cubic centimetre were made, and an additional 1·0 cubic centimetre of 5% emulsion was given subcutaneously. Beyond a slight induration there was no local reaction to the intradermal injection, but the monkey showed a well-marked febrile reaction for four days, beginning six to seven days after inoculation (Figure IV). Blood taken on the ninth day was inoculated into two guinea-pigs. These showed febrile reactions, reaching maximum temperatures of 40·3° C. (104·5° F.), on the tenth day, and 40° C. (104° F.), also on the tenth day. Three weeks later these guinea-pigs showed no reaction to an inoculation of virus which gave typical reactions in control guinea-pigs.

This immunity is taken as the final indication that the animals had been previously infected by the virus. The guinea-pig virus is therefore capable of producing a well-defined pyrexial infection in the monkey, associated with the presence of virus in the circulating blood during the febrile period. The absence of a local intradermal lesion speaks against the virus being of the spotted fever or *tsutsugamushi* types of Rickettsia.

Three monkeys, M.2, M.3 and M.4, were inoculated subcutaneously with infective mouse spleen emulsion. Monkeys 2 and 3 showed temperature reactions of similar type to that given by M.1, but with a notably shorter incubation period. Monkey 3 was visibly sick and ate poorly. Monkey 2, like Monkey 1, showed no symptoms beyond fever. Blood was taken on the third and seventh days and inoculated into guinea-pigs. Blood taken on the third day from Monkey 3 gave a doubtful reaction in the inoculated guinea-pig. Seven-day blood from both monkeys gave a delayed febrile response of typical form with maxima of 41·1° C. (105·9° F.) and 40·4° C. (104·7° F.) respectively, each on the thirteenth day.

Immunity tests on these guinea-pigs have not yet been done.

Specimens of blood were also taken thirteen and twenty days after inoculation to test the power of the serum to agglutinate rickettsial emulsions (see below). Both specimens from Monkey 3 gave good agglutination, the second being active when diluted 1 in 100. The first specimen from Monkey 2 was negative; the second gave incomplete agglutination with undiluted serum.

Monkey 4, inoculated with a different batch of mouse spleen from Monkeys 2 and 3, showed no temperature rise or symptoms over eleven days.

The results, therefore, indicate that three out of four animals became typically infected.

Developing Egg.—Attempts were made to cultivate the virus on the chorio-allantois of the developing egg according to the standard technique used in this laboratory.

After inoculation, the eggs were incubated at a temperature of 35° C. to favour the development of any weakly growing virus. The lesions obtained were very slight and of dubious significance. In the first series of passages, starting with the original D.6 emulsion, membranes from the second passage were inoculated into guinea-pigs. One reacted 40·6° C. (105° F.) on the tenth day and was killed. Its liver was stored in the frozen state and tested for activity six weeks later. The inoculated guinea-pig reacted typically and was used as a source for the series of consecutive guinea-pig inoculations to test cross immunity between guinea-pig and mouse virus strains, which are described below. The other showed no temperature rise, but a subsequent test showed it to be immune, so that the virus had definitely survived two egg passages. The next test at the fifth passage, however, gave completely negative results. Two attempts were made to initiate egg passage strains with heavily infected mouse spleens. Some doubtfully specific lesions were produced on the first membranes inoculated, but nothing was visible on subsequent passages. In one series the third generation membranes emulsified and inoculated into mice produced typical infections with Rickettsiæ in spleen smears. No Rickettsiæ were seen in smears from the egg membranes.

It appears, therefore, that the virus can survive and possibly multiply to a slight extent on the chorio-allantois.

Mice.—Most of our work has been concerned with the results of intraperitoneal inoculation in mice. When an emulsion of infective guinea-pig liver is inoculated intraperitoneally into mice of about 15 to 20 grammes weight, a characteristic picture is seen when the mice are killed seven to ten days later. The liver is enlarged and has a relatively pale opalescent appearance; on rare occasions small hæmorrhages are scattered through its substance. The spleen is enlarged, often greatly so, and appears tense and a uniform deep red in colour. Smears from the cut surface of the spleen, suitably stained, show the presence in variable numbers of intracellularly situated bodies which appear to be typical Rickettsiæ. (See Figures I, II and III.)

A certain proportion of our stock mice show enlarged spleens. Figure VI shows the frequency distribution of the sizes of sixty spleens from mice killed in the course of experiments unrelated to "Q" fever. Most of them were used for influenza virus titrations. They came from the same stock and were kept under the same conditions during experiment as those used for "Q" fever work. The spleen sizes were measured, and the product of the length multiplied by the greatest breadth was taken as the measure of size. As far as possible, mice of 15 to 20 grammes weight were used in all experiments, but they were not weighed, and some mice outside these limits are included in both experimental and control series. The normal mice used to provide the data for Figure VI show a sharp peak in the range 30 to 50. A similar census made four months later, also of mice used in influenza virus titrations, gave a higher average value and a wider distribution of sizes over the range 40 to 70. The cause of these enlarged spleens has not been determined, no bacteria can be cultivated on simple media and no Rickettsiæ can be seen in smears. Subinoculations to other mice do not produce enlarged spleens, nor do the spleens of the passage mice show Rickettsiæ. In Figure VI there is also shown the frequency distribution of the sizes of 34 mouse spleens obtained from experimentally

ILLUSTRATIONS TO THE ARTICLE BY DR. F. M. BURNET AND MISS M. FREEMAN.

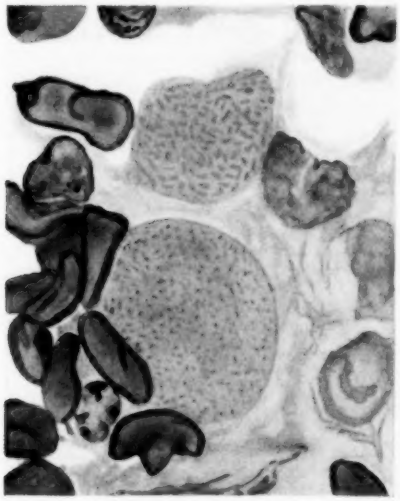

FIGURE I.

Microcolonies of Rickettsiæ as seen in section of infected mouse spleen stained by Mann's method. × 1,200.

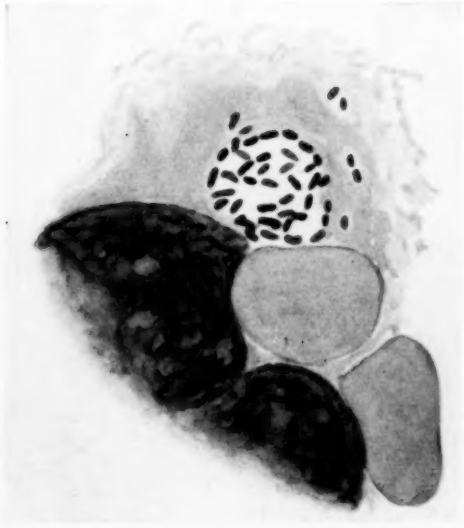

FIGURE II.

A typical small clump of Rickettsiæ in Giemsa-stained smear from mouse spleen. × 2,500.

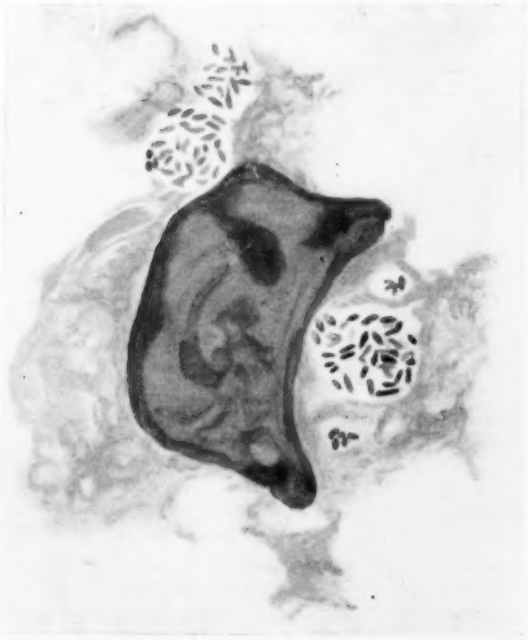

FIGURE III.

Cell showing several small clumps of Rickettsiæ, stained by Castaneda's method. × 2,500.

infected animals, and showing Rickettsiæ in suitably stained smears. As a general rule we may say that if a 15- to 20-gramme mouse shows a spleen of value greater than 100, it has been infected with the "Q" virus. With smaller or larger mice the "upper normal" limit will need modification, but even with very small mice there is a rapid production of great splenic enlargement. A series of 10- to 11-gramme mice inoculated with active material gave, after one week, spleens of 65, 81, 130, 136 and 175 units, all showing Rickettsiæ in smears.

No obvious symptoms have been observed in the mice, and we have encountered only one instance in which the infection seemed to be responsible for the death of the mouse. This mouse died 24 days after inoculation, showing a relatively small, pale spleen and a very pale liver in smears from which numerous Rickettsiæ were found. Mice inoculated in the same series with this one were killed at intervals and examined with the result shown in Table I.

TABLE I.

Results of Inoculation of Mice with Infective Material.

Interval After Inoculation.	Size of Spleen.	Rickettsiæ.
10 days	130	+
	201	+
14 days	181	+
	212	+
21 days	191	+
	246	+
32 days	334	−
	201	?

It will be seen that the spleen size tends to increase progressively.

A few mice have been inoculated intracerebrally under anæsthesia. No symptoms were provoked, but when mice were killed seven to ten days after inoculation the typical large spleens with Rickettsiæ were observed.

Albino Rat.—Young white rats inoculated intraperitoneally with infective guinea-pig or mouse tissues show no symptoms or temperature reaction, but show considerably enlarged spleens when they are killed seven to ten days after inoculation.

Three of a litter of five rats with weights ranging from 85 to 100 grammes were inoculated with an emulsion of infective mouse spleen. All five were killed eight days later. The spleen sizes, expressed as for mice, were: uninoculated controls, 181, 210; inoculated rats, 529, 605, 729. Smears from two of these large spleens showed a few Rickettsiæ on prolonged search. Subinoculation with spleen emulsion for two further passages in 90- to 100-gramme rats gave spleen sizes 285, 316 and 439, 477 respectively. No Rickettsiæ were seen in smears. Spleen emulsion from the third generation was inoculated into mice and a guinea-pig. The results with both species indicated that the virus was present, but in very small amount. The mouse spleens at the seventh day were only slightly enlarged, but all showed a few Rickettsiæ. The guinea-pig showed a rather long incubation period, reaching a peak of 40·8° C. (105·5° F.) on the tenth day.

The Identity of the Guinea-Pig and Mouse Infections.

Although it seemed clear that the infection produced in mice was due to the agent responsible for the febrile reaction in guinea-pigs, we have endeavoured to eliminate any possibility that one or other of the infections represented an activation of some virus or Rickettsia in our normal stock.

In the first place, four different batches of infected guinea-pig liver in the direct guinea-pig series (that is, never having passed through mice) all produced the syndrome in the inoculated mice. Liver from two guinea-pigs inoculated with non-infective bovine blood two weeks before were injected into mice as a control. No splenic enlargement and no Rickettsiæ appeared. Mice inoculated with emulsions of the large spleens found in a proportion of our normal mice did not develop the syndrome.

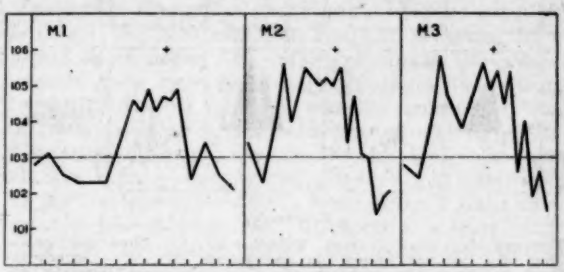

FIGURE IV.

Temperature charts of three monkeys (*Macacus rhesus*) reacting positively after inoculation with "Q" fever virus. *M1* received infective guinea-pig liver emulsion, *M2* and *M3* infective mouse spleen emulsion. + indicates that blood taken on the day shown was infective for guinea-pigs.

The most conclusive proof of the identity of guinea-pig and mouse infections is given by cross immunity tests.

A series of weekly passages was made (*a*) of the direct guinea-pig strain, two guinea-pigs being used for each passage, and (*b*) of a mouse strain, three or four mice being inoculated at each time. One guinea-pig of each lot was killed for passage; the other was kept for a further fortnight and then tested for immunity along with a normal control by inoculation of mouse passage virus.

Six consecutive experiments of this type showed in every case that mouse virus provoked a typical pyrexia in the normal guinea-pig, but no rise of temperature in the one immunized by a previous inoculation of guinea-pig virus.

Figure V shows two typical experiments. Most of the guinea-pigs used as controls in these experiments, that is, inoculated with mouse virus, were subsequently tested for immunity to active guinea-pig virus. They were all immune, but two showed a distinct rise of temperature of short duration, which may indicate that the immunity was not quite complete. Two such tests, one showing a slight pyrexia in the immune animal, are included in Figure V. On the average, the pyrexia induced in guinea-pigs by inoculation of mouse spleen emulsion was higher, commenced earlier, and was more prolonged than that induced by guinea-pig passage liver emulsion.

These cross immunity experiments prove conclusively that the virus responsible for the guinea-pig pyrexia multiplies in the mouse and can be transmitted indefinitely from mouse to mouse. It remains to be shown (*a*) that the guinea-pig virus we have been working with is the same as that present in the blood of human patients which pro-

duced the primary guinea-pig infections; (*b*) what the relationship is between the Rickettsiæ in the mouse spleen and the virus.

To establish the former we forwarded infective mouse spleen to Dr. Derrick for tests to be made in his immune and normal guinea-pigs.

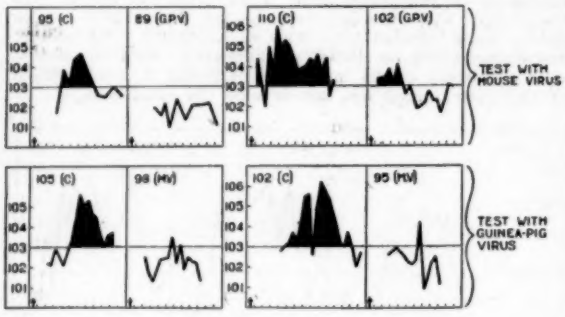

FIGURE V.

Temperature charts from guinea-pigs to illustrate cross immunity between guinea-pig and mouse viruses. Letters in brackets after the number of each guinea-pig indicate its previous treatment. *C*: control normal animal; *G.P.V.*: previously inoculated with and reacting to guinea-pig virus; *MV*: previously inoculated with mouse virus. Time marking in days. Heavy black areas to show significant rise over the normal upper level of guinea-pig temperature—39·4° C. (103° F.).

We are indebted to Dr. Derrick for the following account of the results of his work with this mouse material.

The first lot of mouse spleens sent in February packed with ice were inoculated into two normal guinea-pigs (*D*26 and *D*27) and three immune animals (*D*14, *J*46 and *J*56). *D*26 showed a doubtful reaction maximum temperature of 40·2° C. (104·4° F.). After fourteen days it was killed and liver emulsion was subinoculated to guinea-pig *D*28. This showed no fever, but was subsequently found to be immune. *D*27 also gave a doubtful febrile reaction with a maximum temperature of 40·4° C. (104·8° F.), and on subsequent testing was found to be immune. Two of the immune guinea-pigs showed an immediate febrile reaction for three days not characteristic of "Q" fever; the other (*J*56) gave no reaction.

The results of this series, although indicating that the virus had remained viable, were unsatisfactory, so in April a second batch of two infected mouse spleens (eleventh mouse passage) was sent frozen with dry ice (solid carbon dioxide) in a thermos flask. These were still frozen on arrival in Brisbane, and emulsions were made immediately and inoculated into normal and immune guinea-pigs. The immune animals were larger than the normals and were given a proportionately larger dose. The results obtained from these inoculations indicate that after eleven passages through mice strain *D* produces a sharp fever in normal guinea-pigs, but no reaction in guinea-pigs immune to the strain *J* (derived from another patient). As we have mentioned previously, the incubation period for guinea-pigs inoculated with mouse spleen material is very short, and Dr. Derrick notes that with two of the normal guinea-pigs inoculated with this material the incubation period was only one day—the shortest he has observed.

The question of the relationship between the Rickettsiæ in the mouse spleens and the virus remains to be settled. We believe that the Rickettsiæ represent the actual virus, but we have not been able as yet to find them in guinea-pig tissues. It is always difficult to provide a rigid proof that any formed elements are identical with a virus, unless they can be separated from the infected tissue either by culture or by differential centrifugation or filtration. Our filtrations through gradocol membranes of about 0·7μ average pore diameter (not accurately calibrated, but allowing free passage of vaccinia virus and stopping bacteria) were sometimes negative, and when the results were positive, only small amounts of virus being let through, they are consistent with the particles of the agent, being about the size of the Rickettsia seen in smears.

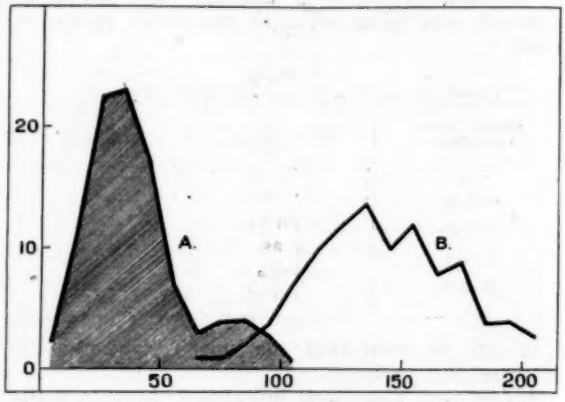

FIGURE VI.

Frequency distribution of sizes of mouse spleens. *A*: normal mice, *B*: mice inoculated with "Q" virus and showing Rickettsiæ in smears. Sizes are expressed as product of length multiplied by the greatest width in millimetres, and the percentage falling in each range of 10, for example, 20-30, 30-40 *et cetera*, is shown. The curves are smoothed by using a moving average over three ranges.

Filtration Experiments.

Three filtration experiments through gradocol type membranes prepared by Mr. J. Graydon, of the Commonwealth Serum Laboratories, have been made. These membranes are of approximately 0·7μ average pore diameter. They are impermeable to bacteria and allow the passage of vaccinia virus.

The first experiments were made with guinea-pig liver suspensions. It was found impossible to render these clear enough to allow more than a cubic centimetre of fluid to pass the filter. Neither of the two guinea-pigs inoculated with each filtrate showed a temperature reaction. Retesting showed the first two animals to be non-immune. The guinea-pigs of the second experiment, however, were both found to be immune. The third experiment was made with an emulsion from guinea-pig spleen. The inoculated guinea-pig showed a typical delayed temperature chart, with a maximum of 40·4° C. (104·7° F.) on the tenth day. It was immune on being retested.

The evidence thus suggests that the virus is filtrable, but that only very small amounts pass through the membranes.

The Rickettsia.

The first indication that rickettsial organisms were concerned in the condition was obtained from a section of mouse spleen stained with hæmatoxylin and eosin. Certain oval areas about the size of a nucleus were observed which seemed to be filled with lightly stained material of faint, uniformly granular texture. They suggested cytoplasmic microcolonies of an organism like the psittacosis virus.

Smears were therefore made and stained by Castaneda's method, and with Giemsa stain. In a high proportion of smears from enlarged and infective spleens bodies which appear to be of rickettsial nature were found, sometimes in enormous numbers.

We have not been able to obtain a completely satisfactory method of staining the organisms. With Castaneda's stain most of them appear blue, but the tint is paler than that taken by psittacosis bodies, and in many clumps a large proportion of the Rickettsiæ are pink. We think it probable that in some of the negative smears such pink-staining Rickettsiæ may be present, but in the absence of associated blue-staining forms it is impossible to distinguish them with certainty. With Giemsa the bodies stain a reddish-purple colour, and in smears from heavily infected spleens they are easily recognizable. When the Rickettsiæ are few in number or are absent as judged by Castaneda-stained films, Giemsa smears are not of much help, since a variety of granules, not unlike the Rickettsiæ, may be found in small numbers in smears from control spleens. In particular, ingested platelets within the cytoplasm of histiocytic cells have a deceptive resemblance to small microcolonies of Rickettsiæ. The following account is based on the appearances observed in smears stained by Castaneda's method.

The organisms take the form of tiny rods less than 1·0μ in length and about 0·3μ across; the shape varies from well-marked rods to coccoid forms indistinguishable from those of psittacosis. When both pink- and blue-staining elements are present in the one group, the pink-staining tend to be larger and less elongated than the blue-staining bodies. In any smear a proportion of the Rickettsiæ will be found extracellularly, but the appearances suggest that all, or nearly all, are initially intracellular, where they give rise to cytoplasmic microcolonies, sometimes relatively sharply defined, at other times with a fairly diffuse distribution of Rickettsiæ through the cytoplasm. Apart from the fact that the great majority of the bodies are definitely rod-shaped, the general appearance of a smear is strikingly similar to that obtained from psittacosis-infected spleens.

Histology of Mouse Liver and Spleen.

The histological appearance of livers from infected mice varies considerably. There is always some diffuse infiltration with cells which appear to be largely of vascular endothelial origin, and a variable number of small inflammatory necrotic foci are present. The liver cells may appear healthy, but usually show some degree of vacuolation. Cells containing characteristic microcolonies of Rickettsia can usually be found without much difficulty. They are always in interstitial cells, presumably Kupffer cells, and their distribution does not seem to be related in any way to that of the inflammatory necrotic foci.

In the spleen sections the only feature which calls for comment is the distribution and character of the Rickettsiæ. These occur as intracellular microcolonies of close-packed individuals, nearly always sharply circumscribed within an oval or circular outline. The accumulations range in diameter from about 3μ to about 12μ. The individual Rickettsiæ cannot as a rule be clearly distinguished, owing to the density of packing, but the general texture of the accumulation makes its nature obvious. With hæmatoxylin-eosin the rickettsial microcolonies stain a rather pale blue of a colder tint than that of the nuclear chromatin. With Mann's stain they are a light reddish-purple. Rickettsial masses occur only in the spleen pulp; the germinal centres (Malpighian nodules), which are practically free from red blood cells, contain none. In the splenic pulp the distribution is very irregular, and one may find numerous infected cells in one area with practically none in any other portion of the section.

Agglutination of Proteus Strains.

Convalescent sera from guinea-pigs and a monkey gave no agglutination of Proteus X19 or Kingsbury strains. Two rabbits inoculated intravenously with mouse spleen emulsion containing Rickettsiæ also failed to develop any agglutinins against these strains. Taken along with Derrick's failure to obtain agglutination with convalescent sera from the human patients, this provides the main evidence that we are dealing with a type of Rickettsia distinct from those known to be pathogenic for human beings.

Agglutination of Rickettsial Emulsions by Convalescent Sera.

Heavily infected mouse spleens contain enormous numbers of Rickettsiæ, and by differential centrifugation with the angle centrifuge it is possible to prepare emulsions in which the majority of the particles are Rickettsiæ. An emulsion of this sort is agglutinated macroscopically by serum from the patient D., from whom the strain was isolated, by three immune monkey sera and by a guinea-pig immune serum. Ten normal human sera, a serum from a known case of endemic typhus with a high titre (1,280) against Proteus X19, a normal monkey serum and several guinea-pig sera failed to react. This work is only in a preliminary stage and technical details will be reported later. Should it be confirmed by further studies, it holds out promise of providing a useful diagnostic procedure.

Discussion.

In all work on virus diseases in which the infection is transferred from animal to animal by

inoculation of crude tissue emulsions, the possibility of the contamination or replacement of the virus by some infective agent latent in the laboratory animals must be constantly borne in mind. We undertook these investigations with the object of studying the agent responsible for Derrick's "Q" fever in man. We must first discuss whether the clinical syndrome "Q" fever in man, the febrile reaction in the inoculated guinea-pig, and the pathological changes which we have observed in the mouse are all due to the same infective agent. The relationship between mouse and guinea-pig infections has been adequately studied, and the evidence of complete cross immunity definitely establishes that the agent responsible for the guinea-pig reactions is indefinitely transmissible through mice. The Rickettsiæ were found in mouse spleen and liver in practically every instance when the tissues were infective, and never in control mice treated in various ways. Conclusive identification of the Rickettsiæ as the infective agent is probably impossible, but the evidence is just as strong in this particular case as in that of any other experimental infection by Rickettsiæ. It would be merely pedantic to labour the possibility that the Rickettsiæ seen were harmless associates of some other pathogenic agent.

The tests carried out with mouse passage material by Dr. Derrick show equally that the mouse virus is antigenically identical with that derived from another human case and propagated as strain *J* in guinea-pigs. Since mice have not been used in the Brisbane work, this proves conclusively that the virus has not been derived from any unsuspected latent infection of mice. The only question remaining, then, is that of the identity of the guinea-pig fever-producing agent with that responsible for the human infection. This is outside our province, but the data given in the preceding paper by Derrick can hardly allow any doubt that they are identical. The only alternative is that some of Derrick's guinea-pigs are infected with a Rickettsia whose activity becomes manifest only after a large intraperitoneal inoculation of blood, but which can be transmitted by inoculation to normal guinea-pigs, producing the characteristic mild fever. Apart from the direct evidence against this hypothesis, such as negative results with human blood from uninfected individuals, there is strong indirect evidence in the absence of any reference in the literature to the occurrence of spontaneous latent rickettsial infections in guinea-pigs. Since this species has been used in enormous numbers for work on all the rickettsial infections of man, any spontaneous rickettsial infections in the guinea-pig could hardly have escaped recognition.

However, the greatest caution is necessary in interpreting apparent transmissions of human infections to animals, particularly in the early stages of research, before easy identification of the agent by immunological tests *et cetera* can be made. There are many well-known mistakes of this sort in bacteriological literature. A recent communication by Laigret (1936) to the Second International Congress for Microbiology suggests that particular care should be taken to make certain that an agent like the one we are concerned with is not derived from the laboratory animals. He states that:

> We have isolated from apparently healthy mice a virus which is not pathogenic for them, but is for the guinea-pig and for the monkey. This same virus has been recovered from human cerebro-spinal fluid . . . . It is highly ubiquitous . . . . It exists in the embryo mouse and in the embryo chick.

This report is available only in abstract, and there are no details to allow an opinion as to whether the so-called ubiquitous virus has any real existence; but the range of activity claimed is much the same as the one we are working with.

We think it highly probable that the virus of "Q" fever is the Rickettsia which we have described, but before this can be asserted with confidence we feel that it should be shown that mice can be infected directly from human material, as well as after passage from guinea-pigs. With this provisional conclusion that "Q" fever is rickettsial, we may consider briefly its relation to the other rickettsial diseases of man.

Modern work on the rickettsial diseases of human beings indicates that three great divisions may be made primarily on cross immunity reactions in guinea-pigs: (i) classical and endemic typhus, transmitted by lice and rat fleas; (ii) *Tsutsugamushi* and scrub typhus, transmitted by mites, and particularly characterized by the power of convalescent serum to agglutinate the Kingsbury strain of Proteus X; (iii) Rocky Mountain spotted fever and the other milder spotted fevers, such as *fièvre bouttonneuse* of the Mediterranean littoral, transmitted by ticks.

It is quite obvious that the infection we are dealing with does not correspond with the type form of any one of these divisions. Examination of the literature, however, shows that in almost every tropical or subtropical country where detailed investigation of human fevers has been made, one or more local types of rickettsial infection have been recognized. If adequate cross immunity tests with the classical types are carried out, all the local types can probably be relegated into one of the three main divisions, but in the absence of such tests it is often very difficult to decide where the agent of a mild typhus-like disease should be placed. Any discussion of the position of "Q" fever in the series must therefore be very tentative until cross immunity tests can be carried out.

The possibilities to be considered are that it is (i) a form of murine endemic typhus, (ii) a fever of the tick-bite group, allied to *fièvre bouttonneuse*, and (iii) an aberrant example of the mite fever group.

Against the first possibility are: (*a*) The absence of X19 agglutination in patients and in inoculated rabbits. Since Australian infections by murine virus are known to be associated with the production of such agglutinins, this provides very strong evidence

against "Q" fever being of this type. (*b*) The fact that no scrotal swelling and no Rickettsiæ in peritoneal smears have been observed in infected guinea-pigs. (*c*) The distribution of Rickettsiæ in the liver and spleen cells in circumscribed microcolonies, which is unlike that described and figured for murine typhus (or indeed for any other rickettsial infection). (*d*) The low grade of pathogenicity for the albino rat.

The tick-bite fevers nearly always produce a local primary lesion and regional lymph gland enlargement which are not seen with "Q" fever. Further, they nearly always show low titre agglutination of one or all of the Proteus X strains. The more actively pathogenic members of the group, such as Rocky Mountain spotted fever and Sao Paulo typhus, are readily transmitted to guinea-pigs, but the Mediterranean type has very low pathogenicity for laboratory animals, and most experiments have been made on human volunteers. We have not found any record of the experimental infection of mice by viruses of this group.

Finally, the *tsutsugamushi* group must be considered. Fevers of this type are known to occur in tropical Queensland, but regularly provoke an agglutination of Proteus XK strains, and usually show a primary sore. Wolff and Kouwenaar (1934) find that Sumatran mite fever virus is pathogenic for white mice, killing on an average in about eleven days and producing changes very similar to those we observe with "Q" fever virus. Their paper has been available to us in abstract only, and we do not know whether the Rickettsiæ in the spleen show the distribution noted with our virus.

As far as can be determined from a study of the literature in the absence of experimental comparison with other types, we incline to regard the Rickettsia responsible as being distinct from any of the three main types. The chief reasons for so doing are: (*a*) the absence of any production of X19 or XK antibodies in patients or rabbits, and (*b*) the morphology of the intracellular microcolonies of Rickettsiæ in spleen and liver cells of the mouse. This opinion can be substantiated or disproved only by direct immunological comparison of the "Q" fever virus with the well-defined types.

Summary.

1. The virus isolated by Derrick from cases of "Q" fever produces characteristic pathogenic effects on monkeys and mice.

2. A well-defined febrile reaction, during which the blood is infective for guinea-pigs, follows subcutaneous inoculation of virus in the monkey.

3. Mice inoculated intraperitoneally show enlargement of spleen and liver with characteristic histological changes.

4. In sections and smears of infected mouse liver and spleen large numbers of rickettsial organisms are visible. These occur in relatively large intracytoplasmic microcolonies.

5. Inoculation of mouse virus into guinea-pigs and monkeys gives a febrile reaction with a very short incubation period. Cross immunity tests indicate that mouse virus is identical with guinea-pig virus.

6. The virus produces an inapparent infection in albino rats.

7. The virus survives, but does not produce characteristic lesions on the chorio-allantois of the developing egg.

8. The virus is filtrable with difficulty through relatively permeable (0·7μ) gradocol membranes.

9. Agglutination of semi-purified rickettsial suspensions by immune human monkey and guinea-pig sera has been observed; this reaction appears to be specific.

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Addendum.

Since this paper was submitted for publication we have had an opportunity, through the kind cooperation of Dr. Derrick, to isolate the Rickettsia by direct inoculation of mice with blood taken from a human patient with typical "Q" fever. Spleen smears from mice killed thirteen days after inoculation showed large numbers of typical Rickettsiæ.

In addition, specimens of serum taken by Dr. Derrick on the twelfth and twentieth days from another patient showed an increase in agglutinating titre for a rickettsial emulsion from 1 in 4 to 1 in 200 during this period.

These two findings appear to provide final evidence of the ætiological rôle of Rickettsia in "Q" fever.

THE FUNCTIONAL PATHOLOGY OF ANÆMIA.

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INTRODUCTION.

IN recent years the attention of hæmatologists has been focussed chiefly upon the morphological changes in the blood in disease, the classification of anæmias, and the nutritional and hormonal factors modifying hæmopoiesis. There is, however, another aspect of anæmia of interest to the clinician, namely, the effects produced by anæmia upon the body and the response of the organism to the altered conditions of its internal environment. A great many uncorrelated observations bearing upon the subject have been made, and in order to stimulate further investigation it would seem desirable to assemble the relevant data and to discuss them in a comprehensive fashion. This is the purpose of the present communication.

DEFINITION OF ANÆMIA.

Anæmia means literally "lack of blood"; but the blood is a complex fluid composed of cellular and non-cellular elements, any one of which may be

lacking without the others being affected. The blood is not a tissue; but the cells of the red series may be regarded as constituting a tissue—the erythron (Boycott[4])—and it is to deficiency primarily affecting the erythron that the term anæmia is applied. Anæmia may, therefore, be defined as a deficiency of red blood corpuscles or their constituents per unit volume of blood. Perhaps a more precise term would be erythranæmia. The word anæmia is not synonymous with oligæmia, which means an abnormally small blood volume; nor should it be employed to signify diminished blood content of a part resulting from changes in the calibre of the blood vessels (ischæmia).

Arrangement of Subject.

The red corpuscles are concerned with the transport of oxygen to the tissues and the removal of carbon dioxide. Anæmia therefore results in a disturbance of the respiratory function. In the presence of progressively increasing anæmia the body may for a time succeed in maintaining its functions by the development of compensatory mechanisms and tolerance towards the changed conditions. If, however, compensation and tolerance are incomplete, symptoms arise; when they fail, disintegration of function and ultimately death may ensue. The subject may, therefore, be dealt with in four parts, namely: (*a*) The transport and utilization of oxygen; (*b*) the transport and elimination of carbon dioxide; (*c*) restoration, compensation, tolerance and failure; (*d*) the symptoms and signs of anæmia.

Part I: The Transport and Utilization of Oxygen.

Absorption of Oxygen From Air.

At sea-level the air we breathe contains 20·9% of oxygen at a pressure of one atmosphere (760 millimetres of mercury), so that the pressure of oxygen in the inspired air is 20·9% of an atmosphere or 152 millimetres of mercury. In the lung alveoli the air becomes diluted with carbon dioxide and saturated with water vapour, so that the percentage of oxygen falls to between 13 and 14 and the pressure of oxygen to about 100 millimetres of mercury.[1] In order to reach the blood, the oxygen has to diffuse across the membrane lining the alveoli. But this membrane offers a certain resistance to the diffusion of gas. Consequently in the short space of time during which the blood is passing through the lungs it does not come into complete gaseous equilibrium with the oxygen in the alveoli. The oxygen tension in the lung capillaries, therefore, remains somewhat below that in the lung alveoli. The resistance of the alveolar membrane to the diffusion of oxygen differs from individual to individual, with the result that the oxygen tension difference between the alveolar air and the plasma of the blood leaving the lung capillaries may vary between 5 and 25 millimetres of mercury. There is, however, no evidence of any interference with the normal diffusion of oxygen across the membrane in anæmia, except in the presence of pulmonary complications, which are rare. This can be shown by examining the oxygen content and oxygen tension of the arterial blood.

Oxygen Content and Oxygen Tension of Arterial Blood.

The oxygen in the blood exists partly in combination with hæmoglobin and partly in physical solution. By far the greater part, however, is in combination with hæmoglobin, only about 1% to 3% of the oxygen being in physical solution; so that the oxygen capacity of the blood, that is, the total amount of oxygen that the blood will take up when exposed to atmospheric air at ordinary pressures (near sea-level) and at room temperatures (15° to 20° C.[3][27]), is determined chiefly by the percentage of hæmoglobin (see Figure I). With 100% hæmoglobin (corresponding to 14·5 grammes of hæmoglobin per 100 cubic centimetres using the American scale) the oxygen capacity is about 20 cubic centimetres per 100 cubic centimetres of blood and of this only 0·62 cubic centimetre is in physical solution at 15° C.[2] When the percentage of hæmoglobin in the blood is less than normal, as in anæmia, there will be a corresponding diminution in the oxygen capacity, that is to say, the amount of oxygen which can be carried in each cubic centimetre of blood will be less than normal. The oxygen content of the arterial blood is, however, not the same as the oxygen capacity, partly because the blood passing through the lungs has been exposed to a pressure of oxygen less than that in atmospheric air and partly because of the difference in temperature. The amount of oxygen which enters into combination with hæmoglobin and the amount which goes into solution will vary according to the pressure of oxygen to which the blood is exposed. If, for example, blood is placed in a tonometer, and after rotation for a sufficient length of time to permit of gaseous equilibration being established, the blood and the atmosphere with which it is in contact are each examined with regard to their

[1] Vapour pressure at 37° C. = 47 mm. Hg. Hence

$$\frac{14\ (\%\ \text{oxygen}) \times 760\ (\text{atmos. press., mm. Hg}) - 47\ (\text{vap. ten.})}{100}$$

= 100 mm. Hg. pressure of oxygen.

[2] *O_2 in Combination with Hæmoglobin.* 1 gramme of Hb when fully saturated will combine with 1·34 c.cm. O_2 (Hüfner[31]), therefore 14·5 grammes of Hb when fully saturated will combine with 19·43 c.cm. O_2.

O_2 in Solution. Solubility of O_2 in whole blood.

Pressure.	Temp.	O_2 in Solution, c.cm. %	
1 atmosphere (760 mm. Hg)	15° C.	3·1	(Bohr[3])
20·9% of an atmosphere (152 mm. Hg)	15° C.	0·62	
1 atmosphere (760 mm. Hg)	20° C.	2·9	
20·9% of an atmosphere (152 mm. Hg)	20° C.	0·58	

O_2 Capacity.

At 15° C. and with 14·5 gm. Hb per 100 c.cm. (100% Hb)	
In combination with Hb	19·43
In solution	0·62
	20·05
At 20° C. and with 14·5 gm. Hb per 100 c.cm. (100% Hb)	
In combination with Hb	19·43
In solution	0·58
	20·01

oxygen content, it is found that a definite relationship exists between the pressure of oxygen in the gas and the oxygen content of the blood. If the oxygen content of the blood is compared with the oxygen capacity, the difference between the two expressed as a percentage is referred to as the oxygen saturation of the blood. Corresponding to any given pressure of oxygen, there will be a certain degree of oxygen saturation of the blood. By exposing a sample of blood to different oxygen pressures in a series of experiments, it is possible to construct a curve in which oxygen pressure is plotted against the percentage saturation of the blood with oxygen. Such a curve is known as the oxygen dissociation curve of blood. The form of the dissociation curve is influenced by a number of factors, such as temperature and the concentration of salts in the blood, but especially by the presence of carbon dioxide which diminishes the affinity of hæmoglobin for oxygen. In order, therefore, to obtain an oxygen dissociation curve under standard conditions it is necessary to expose blood at 38° C. to oxygen in the presence of carbon dioxide at a pressure corresponding to that at which it occurs in the alveolar air, namely, 40 millimetres of mercury (Figure II).

Since the curve shows the relationship between oxygen saturation and oxygen pressure, it follows that if we know the oxygen saturation of a sample of blood, we can, by referring to such a curve, find the oxygen tension[1] to which this degree of saturation corresponds. Examination of the arterial blood in anæmia[15] reveals the fact that the oxygen saturation is normal, namely, 94% to 96%. If the oxygen dissociation curve of anæmic blood was the same as that of normal blood, the oxygen tension of the arterial blood would also be normal, namely, about 80 to 95 millimetres of mercury. Actually, the oxygen dissociation curve may be shifted a little to the right[42] so that the oxygen tension of the arterial blood would be fully equal to, if not above, the normal. In an individual with 100% hæmoglobin (14·5 grammes *per centum*) the oxygen content of arterial blood 96% saturated with oxygen at 38° C. would be about 18·936 cubic centimetres per 100 cubic centimetres of blood.[2]

[1] *Oxygen Tension in Fluids.* If a fluid is brought into contact with a gas, a certain amount of the gas goes into solution in the fluid, depending on the pressure of the gas and its solubility. When a point is reached where the rate at which molecules of gas passing from the gas phase into the liquid phase is equal to the rate at which they pass from the liquid into the gaseous phase (or the tendency of molecules to move in either direction is minimal), a condition of gaseous equilibrium is established and the tension of gas in the fluid is said to be equal to that in the gas in contact with it.

[2] *Oxygen Content of Arterial Blood.* Since 14·5 grammes of hæmoglobin when fully saturated combine with 19·43 cubic centimetres of oxygen, the amount of O_2 taken up at a saturation of 96% will be 18·67 cubic centimetres. At an oxygen pressure of one atmosphere (760 millimetres of mercury) 2·2 cubic centimetres of oxygen will dissolve in 100 cubic centimetres of blood at 38° C. (Bohr[43]). At an oxygen pressure of 95 millimetres of mercury (that of arterial blood) 0·266 cubic centimetres will dissolve at body temperature. Hence the oxygen content of arterial blood, 96%, saturated with oxygen at 38° C. will be made up as follows:

Combined with hæmoglobin	18·670
In solution	0·266
	18·936

In the anæmic individual the oxygen content of the arterial blood will be diminished along with the diminution in hæmoglobin, but the oxygen tension

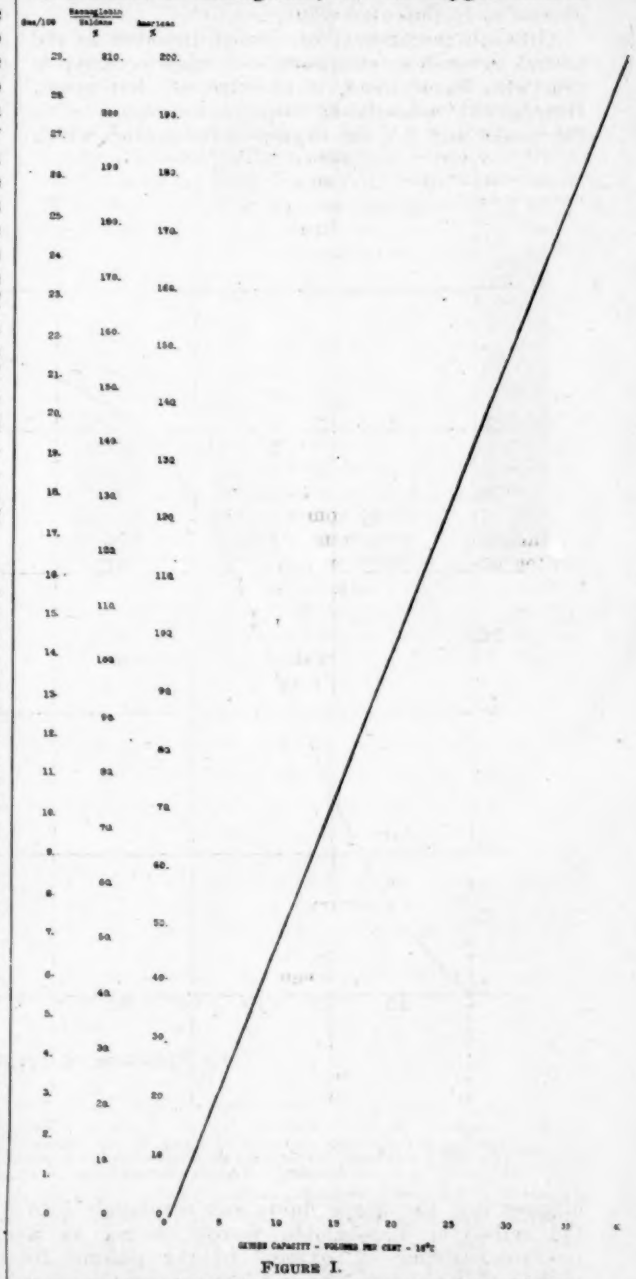

FIGURE I.

Curve showing relationship between oxygen capacity and hæmoglobin content of blood. The changes in the amount of oxygen dissolved in the plasma owing to alteration in the relative volume of plasma and corpuscles were neglected. The hæmoglobin is expressed either in grammes per 100 cubic centimetres or as percentage on the Haldane and on the American scale.

of the blood will be normal. Not only is the oxygen tension normal, but the proportion of oxygen dissolved in the plasma will be somewhat greater

than normal, because oxygen is more soluble in plasma than in corpuscular fluid (Bohr[2]),[1] and in anæmia there is a relative increase in the ratio of plasma to corpuscular volume.

Although the amount of oxygen dissolved in the plasma is small as compared with that in combination with hæmoglobin, it is extremely important. Hæmoglobin actually is nowhere in contact with the tissues and it is the oxygen in the plasma which diffuses into the tissue fluids and ultimately into the cells, the hæmoglobin merely acting as a reservoir, giving off oxygen to the plasma to replace that which is removed. The reverse process occurs in the lungs. Since the oxygen tension and content of the plasma of the arterial blood are normal or above normal in anæmia, it is necessary to enquire whether there is any reason to suppose that the oxygen supply to the tissues should be interfered with in such a condition. It is not, of course, the arterial blood which gives off oxygen to the tissues, but the capillary blood. The problem, therefore, shifts itself next to a consideration of the oxygen content and oxygen tension of the capillary blood.

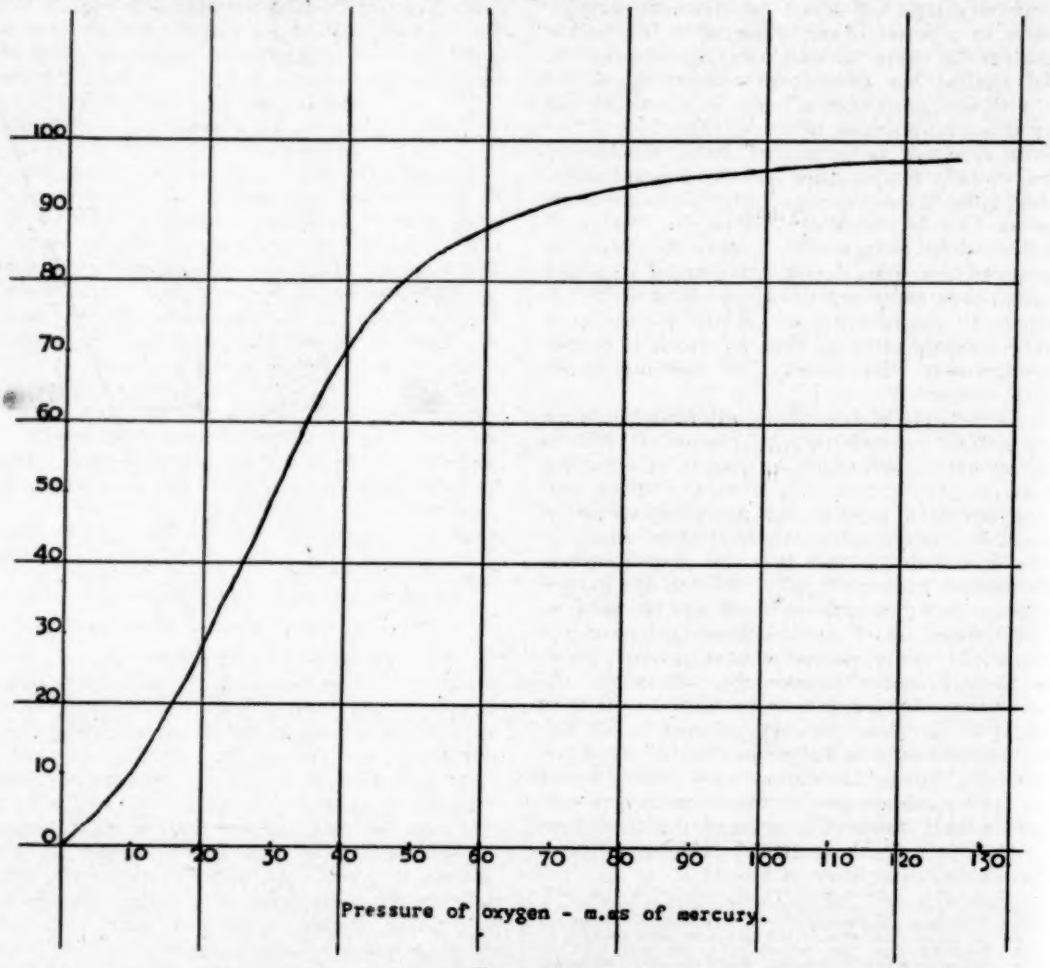

FIGURE II.

The oxygen dissociation curve of blood in the presence of 40 millimetres of mercury pressure of carbon dioxide. Ordinates represent percentage saturation of blood with oxygen; abscissæ, pressure of oxygen in millimetres of mercury. [After Christiansen, Douglas and Haldane (slightly modified).]

Oxygen Content and Oxygen Tension of Capillary Blood.

Although the oxygen tension of the blood as it enters the capillary is that of the arterial blood, namely, 80 to 95 millimetres of mercury, this does not represent the oxygen tension throughout the whole length of the capillary. In the first part of the capillary where the oxygen tension difference between the blood and the tissues is greatest, there is a sharp fall in the oxygen saturation of the blood and, therefore, in the oxygen tension; thereafter the fall is more gradual, so that throughout the

[1] *Solubility Coefficient of O_2* (Bohr[22]). At 760 mm. Hg pressure O_2 and 38° C., 2·3 c.cm. oxygen will dissolve in 100 c.cm. of plasma. At 760 mm. Hg pressure O_2 and 38° C., 1·9 c.cm. oxygen will dissolve in 100 c.cm. of red blood corpuscles. At 760 mm. Hg pressure O_2 and 38° C., 2·2 c.cm. oxygen will dissolve in 100 c.cm. of whole blood.

greater part of the length of the capillary the oxygen tension approaches that of the venous blood. The average capillary oxygen tension is, therefore, not simply the mean of the arterial and venous oxygen tensions; it approximates more closely to that of the venous blood.[1] The venous oxygen tension is clearly the best guide to the average capillary oxygen tension. It is, therefore, necessary to inquire how the venous oxygen tension in anæmia compares with the normal. In passing through the capillaries, the blood in the resting individual normally gives off about one-third to one-fifth of its oxygen, that is to say about 3·5 to 6·5 cubic centimetres of oxygen for every 100 cubic centimetres of blood. Suppose that it gives off 5·5 volumes *per centum* of oxygen, and, to simplify the illustration, let it be assumed that the same volume of oxygen is given off, no matter whether the blood be normal, anæmic or polycythæmic. What will be the effect upon the venous oxygen saturation and tension in each case? The results are shown in Table I and illustrated in Figure III.

It will be seen that after 5·5 volumes *per centum* of oxygen had been removed from normal blood there would still remain a large reserve of oxygen, whereas with increasing degrees of anæmia the removal of the same amount of oxygen would cause a progressive encroachment upon this oxygen reserve. Comparison between the composition of arterial and venous blood also shows that in anæmia there would be a greater percentage fall in oxygen saturation and oxygen tension. The reverse would occur in

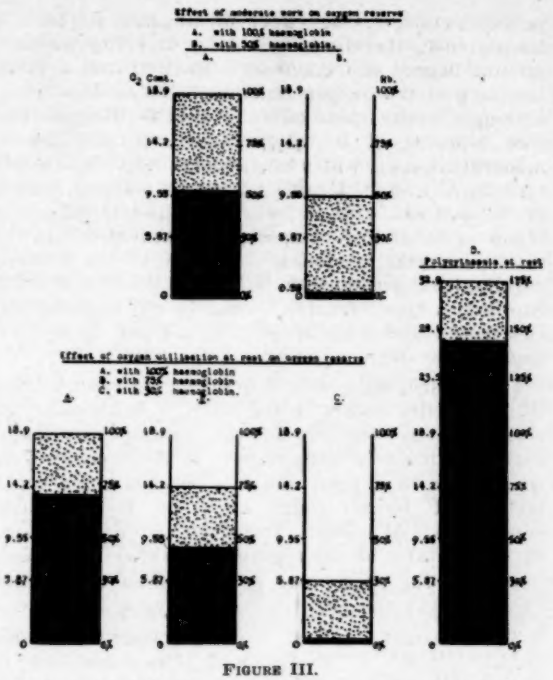

FIGURE III.

Showing the utilization of the oxygen reserve at rest and during work with different percentages of hæmoglobin. The arterio-venous oxygen difference is assumed to be 5·5 volumes *per centum* at rest and 9·0 volumes *per centum* during moderate work.

TABLE I.

Table showing the effect of different percentages of hæmoglobin upon the oxygen content, saturation and tension of venous blood, the fall in oxygen tension and content and the utilization of the oxygen capacity, assuming a constant arterio-venous oxygen difference.

Hæmoglobin. Percentage.	Hæmoglobin. Grms./100.	Oxygen Capacity. Volume Percentage.	Oxygen Saturation Arterial Blood. Percentage.	Oxygen Content Arterial Blood. Volume Percentage.	Oxygen Tension Arterial Blood Millimetres of Mercury.	Arterio-venous Oxygen. Difference Percentage.	Oxygen Content Venous Blood. Volume Percentage.	Oxygen Saturation Venous Blood. Percentage.	Oxygen Tension Venous Blood. Millimetres of Mercury.	Oxygen Tension. Percentage Fall.	Oxygen Content. Percentage Fall.	Oxygen Capacity. Percentage Utilization.
Polycythæmia:												
175	25·4	34·62	96	33·23	96	5·5	27·73	80·1	46	52·0	16·5	15·9
Normal:												
100	14·5	20·05	96	19·25	96	5·5	13·75	67·1	38	60·4	28·5	27·4
Anæmia:												
75	10·9	15·22	96	14·61	96	5·5	9·11	58·7	32	66·6	37·7	36·1
60	8·7	12·28	96	11·79	96	5·5	6·29	51·2	28	70·8	46·6	44·8
50	7·25	10·33	96	9·92	96	5·5	4·42	42·8	23·5	75·5	55·4	53·2
40	5·8	8·39	96	8·05	96	5·5	2·55	30·4	18	81·2	68·3	65·5
35	5·1	7·45	96	7·15	96	5·5	1·65	22·2	14	85·4	76·9	73·8
30	4·35	6·45	96	6·19	96	5·5	0·69	10·7	10	89·6	88·8	85·2
Work:												
100	14·5	20·05	96	19·25	96	9·0	10·25	51·1	28	70·8	46·7	44·9
75	10·9	15·22	96	14·61	96	9·0	5·61	36·9	20	79·2	61·6	59·1
60	8·7	12·28	96	11·79	96	9·0	2·79	22·7	15	84·4	76·3	73·3
50	7·25	10·33	96	9·92	96	9·0	0·92	8·90	9	90·6	90·7	87·1

polycythæmia.[1] One effect of anæmia in such a simple case, therefore, would be to bring about a greater degree of oxygen unsaturation and a great lowering of the oxygen tension in the venous blood. During exercise these effects would be exaggerated. The removal of 9 volumes *per centum* (as in moderate work), which in a normal individual would still leave a considerable reserve of oxygen, would in the patient with 50% of hæmoglobin cause the blood to be almost completely desaturated. If the venous oxygen tension is an index of the average capillary oxygen tension, it follows that the average capillary oxygen tension would in the hypothetical case given above be lower than normal in proportion to the degree of anæmia.

Before accepting this conclusion as representing what actually occurs in the body, it is necessary to scrutinize the validity of the assumptions made, more particularly with regard to the constancy of the volume of oxygen removed per 100 cubic centimetres of blood under each of the specified conditions. We have, therefore, to examine the experimental evidence regarding the effect of anæmia upon (*a*) the percentage utilization of the oxygen capacity, (*b*) the arterio-venous oxygen difference.

The results of all investigators in this field,[40][45][25][47][49][48] with the exception of Plesch,[54] are in agreement in respect of the increased percentage utilization of the oxygen capacity in anæmia (Figure IV).

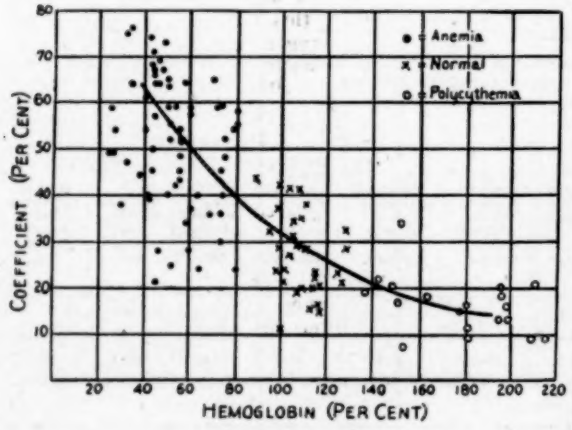

Figure IV.

Curve showing the percentage utilization of the oxygen capacity with varying percentages of hæmoglobin. [After Means (*Medicine*, Volume III, 1924).]

Plesch considered that the increase in the circulation rate prevented this increase, but his values for the cardiac output appear to be extremely high. The increased utilization of the oxygen capacity can be shown not merely by comparing the oxygen capacity with the oxygen content of venous blood, but also by the relationship between the oxygen consumption and the oxygen capacity.[41] The ratio

$$\frac{\text{Basal metabolism in litres of } O_2 \text{ consumed per hour per square metre of body surface} \times 100}{\text{Oxygen capacity,}}$$

which is normally about 40, may increase in anæmia to about 200. As regards the arterio-venous oxygen difference, that is to say, the amount of oxygen given up to the tissues per unit volume of blood passing through them (expressed as cubic centimetres of oxygen per 100 cubic centimetres or per litre of blood), the conclusions of different observers are not in agreement. According to Lundsgaard,[45] the conditions which obtain in the body are such as have been represented in the example described above, namely, that at rest the blood gives up on an average about 5·5 volumes of oxygen per 100 cubic centimetres of blood, no matter whether the oxygen capacity be normal, increased, or diminished, provided always that the oxygen capacity does not fall below 5·5 cubic centimetres *per centum*. That is to say, he maintains that so long as the oxygen capacity remains above 5·5 volumes *per centum*, the arterio-venous oxygen difference is independent of the oxygen capacity. Should the oxygen capacity fall below 5·5 *per centum* (corresponding to a hæmoglobin value of 25 *per centum*), the only means by which the tissues could be supplied with the same amount of oxygen per minute would be an increase in the cardiac output, but above this level there would be no need for such a compensatory mechanism. Harrop[25] came to a similar conclusion. These results in anæmia are paralleled by the observation of Greene and Greene[21] on the arterio-venous oxygen difference in the dog at different stages of anoxæmia produced by breathing diminishing amounts of oxygen. According to these observers, the arterio-venous oxygen difference (and the oxygen consumption) remain practically unchanged until the venous blood is completely reduced. Both Lundsgaard and Harrop based their conclusions upon the results of examination of venous blood obtained by puncture of a vein at the elbow. Harrop also compared the oxygen content of elbow vein blood with that of arterial blood obtained by puncture of the radial artery. The oxygen content of blood drawn from the elbow vein does not, however, necessarily represent the oxygen content of the mixed venous blood returning to the heart from all parts of the body; and this may account for the discrepancies between the findings of Lundsgaard and Harrop and those of other investigators,[54][55][40][57] whose results depend upon various rebreathing procedures for equilibration of the mixed venous blood with air in the lungs, combined with a determination of the respiratory exchange. Such procedures enable one to calculate the cardiac output and the oxygen consumption per minute, and from this the amount of oxygen consumed per 100 cubic centimetres of blood passing through the tissues. These methods, when applied to the study of anæmia, have yielded results which indicate that there is a general tendency for the arterio-venous oxygen difference to diminish *pari passu* with the diminution in oxygen

[1] This does not necessarily hold true of all cases of polycythæmia, as in some cases the oxygen saturation of the arterial blood is less than normal.

capacity (see Figure V); but owing to various complications such as fever and failure of the circulation which may arise in the course of disease causing anæmia, this relationship does not regularly obtain.

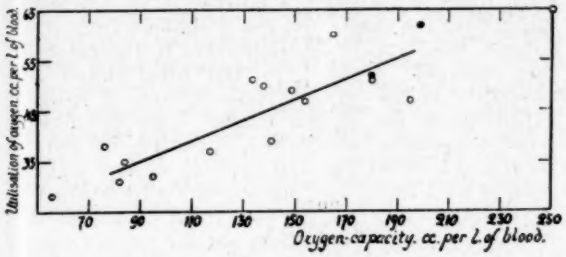

FIGURE V.

Curve showing the utilization of oxygen in cubic centimetres per litre of blood (the arterio-venous oxygen difference) with varying oxygen carrying-capacity of the blood. [After Liljestrand and Senström (*Acta Medica Scandinavica*, Volume LXIII, 1925).]

As regards the effects of anoxæmia produced by breathing atmospheres deficient in oxygen, the experiments of Gollwitzer-Meier[20] on dogs have yielded results which differ from those of Greene and Greene, cited above, in showing a diminution in the arterio-venous oxygen difference in the presence of progressively induced anoxæmia. Grollman's[22] observations upon the human subject are also in agreement with these findings. The evidence as a whole, therefore, points to the conclusion that anæmia and arterial anoxæmia are both accompanied by a diminution in the arterio-venous oxygen difference; but it is owing to the greater percentage utilization of the oxygen capacity (or the oxygen content of the arterial blood) that the venous oxygen saturation, and therefore the venous oxygen tension, falls to a lower level than normal. From this it may be inferred that the average capillary oxygen tension is also lower than normal. It is now necessary to inquire into the significance of the diminished arterio-venous oxygen difference and the possible effects of the low average capillary oxygen tension. The diminished arterio-venous oxygen difference might be due either to an increased cardiac output or to diminished oxygen consumption, or both together. The first of these factors will be dealt with more fully in Part III; the second, in so far as it concerns the unloading of oxygen from the blood, will be considered here.

The Unloading of Oxygen from the Blood and the Consumption of Oxygen in the Tissues.

It is not easy to decide from a determination of the total oxygen consumption of the body exactly what effects anæmia has on tissue respiration, since the oxygen consumption might be increased in certain organs, such as the heart and muscles of respiration, which are concerned with compensatory changes, but diminished in other parts of the body. The question has, therefore, to be approached from the point of view of the mechanism of the unloading of oxygen and the possible effects of disturbances of this mechanism upon tissue respiration.

It may be stated in the first place that there is no evidence of any inability on the part of hæmoglobin to yield up its oxygen in anæmia. This possibility is excluded by reference to the oxygen dissociation curve of hæmoglobin. Since the blood undergoes greater desaturation in anæmia than normally, oxygen tensions will rapidly be reached which correspond to the steep part of the dissociation curve. The steepness of the curve indicates that hæmoglobin gives up its oxygen more readily than it does at higher oxygen pressures. Even at very low oxygen tensions when the blood is almost completely reduced, it parts with its oxygen as readily as it does over the range of oxygen tensions which normally obtain at rest.

Two additional factors may be present in anæmia, both of which would result in a diminished affinity of hæmoglobin for oxygen, namely, a shift of the oxygen dissociation curve to the right[41] and an increase in the concentration of carbonic acid in the red corpuscles in the peripheral blood (*vide sequente*). Since any disturbance of the unloading of oxygen which may occur in anæmia cannot be related to a change in the affinity of hæmoglobin for oxygen, it is necessary to inquire what effect will be produced by the lowered average capillary oxygen tension.

The consumption of oxygen in the tissues would, in the absence of replacement of this oxygen, lead to a fall in tissue oxygen tension, ultimately to zero. Since, in accordance with the gas laws, oxygen diffuses from a point of higher pressure towards one of lower pressure, this fall in pressure would lead to the passage of oxygen from the blood plasma, through the capillary walls, into the tissue fluids and so into the tissue cells. The fall in oxygen tension in the plasma which results from loss of oxygen to the tissues, in turn causes hæmoglobin to give off more oxygen in accordance with the law represented by its oxygen dissociation curve, the oxygen thus dissociated going into physical solution. There is, therefore, a gradient of oxygen pressure from the corpuscles to the tissue cells. The rate at which oxygen diffuses out of the capillaries depends upon the steepness of the gradient, that is to say, upon the difference between the oxygen tension in the plasma and that in the tissues.

The first question to be settled is under what conditions and to what extent does the oxygen tension in the plasma affect the oxygen supply to the tissues and the oxygen consumption. Every capillary may be regarded as supplying oxygen to a certain mass of tissue which in the case of resting mammalian muscle is estimated by Hill[30] to be about twelve times its own volume. Krogh, having determined the rate at which oxygen diffuses in muscle,[34] the dimensions of the muscle capillaries and the distance between open capillaries at rest,[35][36][37] calculated (with Erlang) that at the boundaries between the zones supplied by capillaries the oxygen pressure would approach zero. Normally, however, the size of these hypothetical anaerobic areas must be negligible, and if anaerobic metabolism and oxygen debt are not to

be set up anywhere in the tissue, the whole of the latter must have a partial pressure of oxygen greater than zero. If anaerobic metabolism prevailed to any significant extent in normal muscle, this would lead to the accumulation of lactic acid, for the lactic acid formed in the course of muscle metabolism would fail to undergo oxidative removal;[12][13][14][28][29] but it has been shown by Simpson and Macleod[60] that the amount of lactic acid in normal resting muscle is exceedingly small, from which it may be concluded that the oxygen tension throughout the tissue is above zero.

Provided that the number of molecules of oxygen reaching the cells is at least as great as the number of molecules of oxygen necessary to meet the demand of the cells for oxygen, the actual tension of oxygen in the cells does not appreciably affect the oxygen consumption. It has been found by numerous observers[38][56][44][16][58][61][42][9][59][2] that breathing atmospheres rich in oxygen, which results in a rise in the tissue oxygen tension above normal,[6] causes little, if any, rise in the oxygen consumption. Just as the oxygen consumption is unaffected by changes in oxygen tension, provided that the oxygen tension remains positive throughout the tissue, so also is the oxygen tension difference between the blood and the tissue, and consequently the rate of diffusion of oxygen out of the blood, unaffected. Suppose, for example, that the average capillary oxygen tension was 30 millimetres of mercury and the average tissue oxygen tension 20 millimetres of mercury, giving an oxygen tension difference of 10 millimetres of mercury. If now the capillary oxygen tension was reduced to 20 millimetres of mercury and the tissue oxygen tension to 10 millimetres of mercury, there would still be a difference of 10 millimetres of mercury, and, therefore, the rate of diffusion would be unchanged. Reasoning along these lines, but in the reverse order, Verzár came to the conclusion that in certain tissues, such as those of the salivary gland, the tissue oxygen tension must be everywhere positive, since a change in the oxygen tension in the blood is not necessarily accompanied by a change in the oxygen consumption. Suppose, however, that the average capillary oxygen tension fell to such a low level that the number of molecules of oxygen per unit volume entering the tissues was so small that the oxygen was all consumed before it had reached the parts of the tissue most distant from the capillary, then anaerobic areas would appear in the outlying parts. These anaerobic areas would occur first opposite the venous end of the capillaries, and with a further fall in the plasma oxygen tension they would spread towards the arterial end. (See Figure VI.)

Since the utilization of molecular oxygen would cease in the anaerobic areas, the oxygen consumption in the tissue would decrease; and the more extensive the anaerobic area, the greater would be the fall in oxygen consumption. It is clear that under these conditions the oxygen consumption would vary with the average capillary oxygen tension and so likewise would the rate of diffusion, since the oxygen tension difference between the plasma and the anaerobic areas would depend entirely upon the capillary oxygen tension, the tension in the anaerobic areas being constant at zero. If this reasoning is correct, the variation of the oxygen consumption with the oxygen tension, when there is no longer a positive oxygen pressure throughout the tissue, receives a simple explanation, namely, the increase or diminution in the extent of the anaerobic areas. On the other hand, the constancy of the oxygen consumption, in spite of variations in the oxygen tension when the oxygen tension remains everywhere positive is not so readily accounted for, and appears at first sight to conflict with the law of mass action (Thunberg[64]). According to this law, the velocity of oxidation, that is, the oxygen consumption, should vary with the number of reacting molecules. Therefore, if the molecular concentration of oxygen was to diminish, there should be a corresponding reduction in tissue oxidation unless the number of molecules of oxygen were in any case far in excess of the number which could combine. Oxidations within the animal body are not, however, such simple processes, but take place, as a rule, by a number of intermediate stages, many of which are controlled by the action of specific enzymes. Each reaction in the series has its own "specific velocity", and the velocity of the whole process will depend upon the slowest of these intermediate reactions. Oxygen may enter into one or more of these reactions, but unless the one in which it is involved is the slowest or becomes the slowest of the series, the molecular concentration of oxygen will have little effect upon the aggregate velocity.[33] It is understandable, therefore, why the oxygen consumption should be relatively independent of the oxygen supply, provided that the supply is at least adequate. This is in agreement with the principle enunciated by Pflüger,[53] according to which the oxygen consumption is within wide limits, determined not by the supply but by the demands of the tissues.

Figure VI.

Illustrating the effect of low oxygen tension in the blood upon the oxygen tension in the mass of tissue supplied by a single capillary. The blackened area represents a portion of tissue in which the oxygen tension is positive; the light portion represents an anaerobic area.

It is possible that both of the above-described types of chemical oxidation take place within the body, the first being simple oxidation processes governed by mass action and readily influenced by changes in oxygen tension, and the second complex chain reactions less readily affected by variation in the oxygen tension. Certain tissues in the body are very sensitive to slight changes in oxygen tension, even although their oxygen consumption may be very small—so small as to make very little difference to the total respiratory exchange. Among

these are the cells of the nervous system, the carotid body and the capillaries. These tissues are capable of reacting in such a way as to bring into play protective mechanisms which ward off the more serious effects of oxygen lack. This is well illustrated in the capillaries and has an important bearing upon the present discussion. A cross-section of muscle shows capillaries lying between the muscle fibres and running parallel to them.[35] At rest, only a few of these capillaries are patent, and each, as already explained, supplies a zone of muscle around it, in which the oxygen pressure progressively diminishes as the distance from the capillary increases. (See Figure VII.)

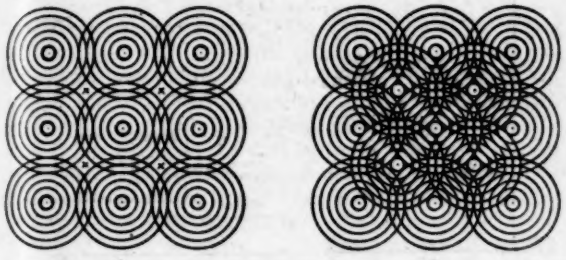

FIGURE VII.

A: Area with nine open capillaries. Each concentric circle is supposed to represent a drop of 5 millimetres of mercury oxygen pressure from that in the capillary, which is 30 millimetres. The *X*s represent areas of no pressure. *B*: Thirteen capillaries in the same area. Most of the tissue is supplied from more than one capillary. No areas of zero pressure. [After Barcroft ("The Respiratory Function of the Blood", Part I, 1925).]

As the oxygen at the periphery of the zone approaches zero, a fall in capillary oxygen tension would tend to cause the development of anaerobic areas and a diminution of the oxygen consumption. This, however, is prevented by a delicate adjustor mechanism which causes more capillaries to come into action, thereby diminishing the distance over which oxygen has to diffuse and maintaining the oxygen pressure throughout the tissue.[36] Krogh and Rehberg[37] have shown that oxygen lack produced by breathing atmospheres deficient in oxygen leads to dilatation of capillaries. This reactive hyperæmia occurs most readily in the skin and in the muscles, but is not observed in the intestines. There has been much discussion as to the nature of the effective stimulus to capillary dilatation. Experiments, such as those of Lewis,[39] based upon the effects of circulatory stasis and the action of products of muscular activity (lactic acid, carbon dioxide *et cetera*) which accumulate in concentration in the tissues and which cause capillary dilatation, are perhaps misleading, for capillary dilatation can occur in the presence of anoxæmia even when the capillary circulation is free,[37] and under such conditions diffusible metabolites derived from the muscle would be rapidly swept away. The rapidity with which the effect may be produced suggests that the changes responsible for the dilatation occur within the capillary itself. Possibly the lowering of oxygen tension in the capillary alters the character of the metabolism in the cells which control the calibre of capillary walls, either directly or through the liberation within them of some metabolite which cause relaxation. According to Krogh[36][37] the Rouget cells are those responsible for the contractibility of capillaries, but Florey[15] considers that they are too few in number to be the sole agents and he would refer the function to the endothelial cells of the capillaries in general. The dilatation probably begins at the venous end of the capillaries where the oxygen tension is lowest and spreads towards the arterial end. The immediate response of capillaries to slight changes in oxygen tension would appear to be a compensatory mechanism which comes into play before the oxygen tension falls to the level at which the products of anaerobic metabolism in muscle, such as lactic acid,[12][13][14][28][29] appear (although these, too, cause vasodilatation), and, indeed, it serves to prevent the oxygen tension from falling to such a level.

Since it has been shown that capillaries are sensitive to changes in oxygen tension and that anæmia is a condition in which the oxygen tension in the capillaries is lowered, it may be inferred that capillary dilatation would, other things being equal, tend to occur in that condition also, especially in the more active tissues, such as muscle, in which the oxygen consumption is greatest, and in which the oxygen tension would consequently diminish most rapidly. Should the protective mechanism fail, or should the capillary oxygen tension fall to such a low level that the opening up of capillaries no longer suffices to maintain a positive oxygen pressure throughout the tissues, the oxygen consumption, as already explained, would fall and it would vary with the oxygen tension in

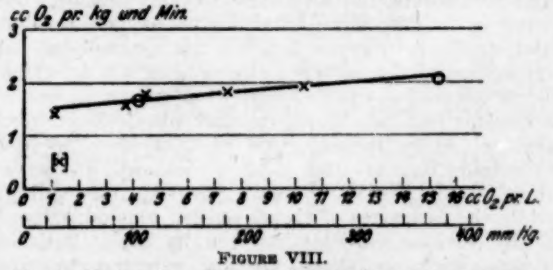

FIGURE VIII.

Curve showing the effect of changes in oxygen pressure upon the oxygen consumption in the carp at 20° C. [After Gaarder (*Biochemische Zeitschrift*, Volume LXXXIX, 1918).]

the blood plasma. This phenomenon may be observed in some animals in which the capillaries supplying the muscles are very few and widely separated. For example, Gaarder,[19] in experiments upon the carp, found that the oxygen consumption rose and fell slightly with changes in the oxygen tension in the water.[1] (See Figure VIII.)

[1] Another factor which would render the penetration of oxygen deeper into the tissues in the carp, even if oxygen tension in them was zero, is the low oxygen tension at which the hæmoglobin of this animal becomes saturated, namely, 10 millimetres of mercury. If the hæmoglobin was 60% saturated, the oxygen tension would be only 2 millimetres of mercury, so that the diffusion pressure would be very low.

Again, Verzár,[65] who investigated the oxygen consumption in the denervated gastrocnemius muscle of the cat *in situ*, thought that he had obtained evidence that (even normally) the oxygen tension in parts of the muscle must be zero, since the oxygen consumption changed as the oxygen tension in the blood supplying the muscle was altered by causing the animal to breathe atmospheres containing different amounts of oxygen. A scrutiny of his protocols shows, however, that in those experiments in which a diminution in the oxygen consumption was observed, the oxygen tension in the arterial and venous blood had fallen to or below what we shall see is the critical level at which changes in tissue respiration resulting from oxygen lack appear. What is this critical level?

Tissue Oxygen Tension and Oxygen Consumption.

It has been repeatedly shown in experiments, both on man and animals, that the breathing of atmospheres deficient in oxygen, whether by living in a pneumatic chamber under reduced pressure[42][43][66][26] or by inhaling gas mixtures containing low percentages of oxygen[61][42][9][18][63][22][23] causes little, if any, change in the oxygen consumption until the oxygen in the atmosphere is reduced to about 76 to 90 millimetres of mercury, corresponding to about 10% to 13% of oxygen at ordinary atmospheric pressures. Indeed, a slight initial rise in oxygen consumption is frequently observed; but when allowance is made for the increased work of the heart and muscles of respiration, this is converted into a slight decrease. Since the arterial anoxæmia caused by lowering of the oxygen tension in the inspired air must cause a fall in the capillary oxygen tension and ultimately in the tissue oxygen tension, the issue is to determine what tissue oxygen tension and capillary oxygen tension correspond to the critical oxygen tension in atmospheric air at which a lowering of oxygen consumption begins to occur. The older methods of determining the tissue oxygen tension, as by the injection of dyes[10] or by the determination of the oxygen content of secretions,[51][52][24][62][7] have proved misleading, while the estimates of tissue oxygen tension arrived at by various calculations and by other indirect means, such as those already referred to, are uncertain. Campbell,[5] however, has devised a method of determining the tissue oxygen tension more directly, by the injection of air between the skin and the muscles or into the peritoneal cavity of rabbits and analysing the air after allowing sufficient time for it to come into gaseous equilibrium with the tissues in contact with it. Normally the oxygen tension between the skin and the muscles was found to be about 20 to 30 millimetres of mercury, and in the peritoneal cavity 30 to 40 millimetres of mercury. When, however, the animal was made to breathe an atmosphere containing only 11% of oxygen, the oxygen tension under the skin was reduced to about 14 millimetres of mercury, and in the peritoneal cavity to about 27 millimetres of mercury, while at the same time the oxygen consumption diminished by about 28%.[6] In experiments upon the effects of anæmia upon tissue oxygen tension, Campbell[7] obtained results which show that tissue oxygen tensions approaching these low values begin to occur in the same situation in some animals when the hæmoglobin in the blood falls to about 50%, although a lowering of hæmoglobin percentage below this level is not necessarily accompanied by further lowering of oxygen tension. (See Figure IX.) It appears, therefore, that the critical

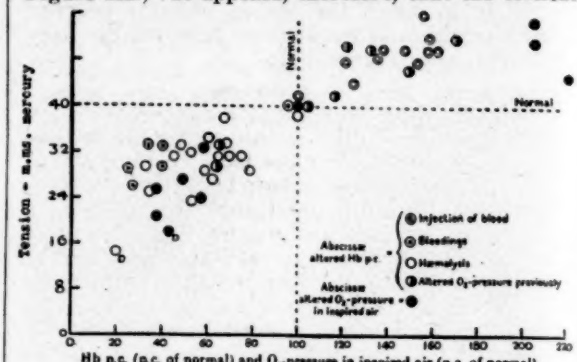

FIGURE IX.

Illustrating (i) the relation between hæmoglobin percentage and oxygen tension in the abdominal cavity of the rabbit, and (ii) the relation between oxygen pressure in the inspired air (percentage of normal) and oxygen tension in the abdominal cavity in millimetres of mercury. [After Campbell (*Journal of Physiology*, Volume LXV, 1928), slightly modified.]

tissue oxygen tension at which tissue respiration becomes impaired varies in different tissues, but lies between 14 and 27 millimetres of mercury, or perhaps somewhat above this level; while the critical percentage of hæmoglobin at which these changes are liable to make their appearance is approximately 50%. Unless compensatory changes occur to prevent the tissue oxygen tension from falling to or below this level, a diminution in oxygen consumption is to be anticipated. The venous oxygen tension which would be found with hæmoglobin values of 50% would, of course, vary with the arterio-venous oxygen difference; but reference to the table shows that with an arterio-venous oxygen difference of 5·5 volumes *per centum* it would be 23·5 millimetres of mercury for the mixed venous blood, which is well within the range of tissue oxygen tensions observed in Campbell's experiments. In view, however, of the diminished arterio-venous oxygen difference and the shift of the dissociation curve of oxy-hæmoglobin to the right in anæmia, the figure should be somewhat higher than 23·5 millimetres of mercury. In all probability the oxygen tension of the blood leaving the tissues in conditions of oxygen lack is very close to the tissue oxygen tension, because of the opening up of capillaries which, by diminishing the distance over which oxygen has to diffuse, favours the rapid establishment of gaseous equilibrium between the blood plasma and the tissues. The venous oxygen tension will, therefore, be very little above the tissue oxygen tension,

and it will also differ little from the average capillary oxygen tension. We may conclude, therefore, that the critical level of oxygen tension in the mixed venous blood below which significant changes in tissue oxidation may occur, is, at the highest estimate, approximately 27 millimetres of mercury. If hæmoglobin values of less than 50% do not cause a lowering of metabolism, it may be inferred that this is due to some compensatory mechanism or to some complication which prevents the change. These factors will be dealt with in Parts III and IV of this paper.

We are now in a position to give at least part of the answer to the questions raised earlier regarding the oxygen consumption and the arterio-venous oxygen difference. The conditions under which anæmia might be expected to cause a fall in oxygen consumption, at all events in parts of the body, if not in the body as a whole, have just been described. Two factors which have been under discussion may partly account for the fall in arterio-venous oxygen difference: the opening up of capillaries and the fall in oxygen consumption. The first of these acts, by raising the oxygen tension in the tissue and diminishing the tension difference between the plasma and the tissue, with the result that the oxygen tension in the plasma falls less than it would otherwise fall. It is not necessary to assume an increase in the velocity of blood flow in the capillaries to account for the diminished arterio-venous oxygen difference, although the shortening of the time during which the blood would lose oxygen in its passage through the tissues would at first sight seem to offer a very simple explanation. The increase in the number of active capillaries would, however, be sufficient to explain both the increased volume of blood passing through the tissues and the diminution in the arterio-venous oxygen difference.

Lactic Acid and Anaerobic Muscle Metabolism.

Since anæmia is capable of causing oxygen lack in the tissues, it might perhaps be expected to cause a rise in the lactic acid in the blood, due to the imperfect oxidative removal of that acid in muscles,[12][13][14][28][29][30] as in mountain sickness[1] and in advanced cases of failure (retardation) of the circulation.[11][46] The lactic acid values found even in profound anæmia are, however, at the upper limit of normality,[32] so that other factors must be looked for to account for these findings. These will be considered later in connexion with the phenomena of compensation and tolerance. Muscular exercise should exaggerate all the effects of imperfect oxygen supply which have been described, and cause the rapid development of oxygen debt and lactic acid acidosis. Neuschloss,[50] who made a few observations on the effect of exercise on dogs rendered anæmic by bleeding, found that some of the animals developed an acidosis which, he suggests, may have been due to lactic acid, but he did not actually estimate the lactic acid. It is noteworthy, however, that anæmia does not lend itself to the study of the effects of muscular exercise on metabolism, since fatigue, chiefly of central origin, appears to be the factor limiting muscular effort, thereby preventing the principal development of oxygen debt.

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Reviews.

MNEMOTHERAPY.

A desire to diffuse more rapidly the knowledge of his theories has been responsible for this translation into English of "A Theory of Cancer and Mnemotherapy", by Dr. Rudolf Roosen.[1] The author regards cancerous growth as due to slow, long-continued changes in swelling pressure. Such a change is never completely reversible, as in acute inflammation, but is "always irreversible to the extent of a fraction, though this fraction can be admitted a small one". The process is regarded as analogous to that which occurs in memory, since a stimulus creates not merely a temporary change, but also a permanent alteration (the engramm).

Dr. Roosen plans his attack on two lines: the exhibition of isamin blue acts as an astringent, whilst mnemic therapy increases the defensive mechanism by psychic means. The author, like Groddeck, believes in the therapeutic usefulness of the subconscious, which he calls the psychoid, as distinct from the psyche. Mnemotherapy aims to mobilize the psychoid. Just how this is accomplished is obscure. One gleans that the patient must be told the truth about the nature of the complaint. He must use narcotics sparingly. The practitioner must be content with such therapeutic crumbs and wait for a further instalment.

In spite of obvious deficiencies, the book is worth reading as a reminder of the widespread nervous integration which must participate in the cancer problem.

Notes on Books, Current Journals and New Appliances.

PEARLING IN AUSTRALIAN WATERS.

Ion L. Idriess, in his search for romance in the more remote parts of Australia, has passed from the central goldfields to the pearl seas of the far north-west, and has produced a book which is a strange blend of history and fiction, geography and anecdote, economic speculations and technical descriptions of the work of the men who seek the pearl-shell in dangerous tropical waters.[2] The opening chapters are devoted to the story of the discovery of a superb pearl, which was stolen by a Manilaman diver, but the thread of narrative, upon which are hung anecdotes of life at Broome and in the luggers, is abruptly snapped in a manner which leaves the reader unsatisfied, and we are given vivid but disconnected accounts of divers and diving, hurricanes, wrecks, and adventures on and under the sea. For a time the book becomes the biography of Con, the coloured hoodoo man. Later we find exciting tales of under-water encounters with whales, sharks and other strange monsters. The final chapters tell of the Japanese riots of 1920 and of the present economic position of the Australian pearling industry.

As the author states in his preface, here is material for many books. In putting so much into one volume he has attempted a large task, but although he has arranged his excellent matter in a disjointed fashion, which is always irritating, he succeeds in being both entertaining and instructive.

The photographs which illustrate the book are well chosen and of great interest, but might have been better reproduced and displayed in a more attractive manner.

[1] "A Theory of Cancer and the Practitioner and Mnemotherapy", By D. Roosen, M.D.; English Translation revised by C. F. Marshall, M.D., F.R.C.S.; 1936. London: Baillière, Tindall and Cox. Crown 8vo, pp. 81. Price: 3s. 6d. net.

[2] "Forty Fathoms Deep", by Ion L. Idriess; 1937. Australia: Angus and Robertson Limited. Crown 8vo, pp. 353, with illustrations. Price: 6s. net.

The Medical Journal of Australia

SATURDAY, AUGUST 21, 1937.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: Initials of author, surname of author, full title of article, name of journal, volume, full date (month, day and year), number of the first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction, are invited to seek the advice of the Editor.

DENTISTRY IN THE COUNTRY.

If man is to be a healthy animal, he must be able to obtain, cook, eat and absorb suitable food. Native races such as the Australian aborigines often find this extremely difficult. Under modern conditions man's needs are more easily met, and even those who are forced to live on what is known as the dole are able to obtain food, though there is much room for improvement in both the quality and the quantity of what they receive. The process of evolution provided man with teeth so that he could break up the food that he ate, and mix it with saliva before he sent it on its long and somewhat involved journey. By experience man has learned that the assimilation of food by his body is made easier by the teeth that are a nuisance to him in his childhood because he forgets to clean them and a trial to him in his manhood because they decay. Man has met the problems of caries first of all by creating a dental profession to correct abnormalities, and secondly by trying to discover the causes of caries that he may prevent them. Caries, like many bodily ailments, is not yet generally preventible, and the members of the dental profession increase in number and their science grows apace.

Dental science and its practice are becoming more and more complex. This is due largely to progress in knowledge of dental pathology, and also to the discovery of materials or combinations of materials for dental fillings suitable for use under certain conditions, and to the elaboration of new methods of treatment. The ease with which occult dental caries may be discovered by the use of a photographic film and an X ray machine is sufficient evidence of progress in the practice of dentistry. Continual research is being carried out on materials for the filling of dental cavities, research demanding the highest skill and devotion, and research just as intricate as any of the biochemical researches carried out by medical investigators. Unfortunately, many of the advances in dental science call for the installation of new apparatus in the dental surgery, and this means an increase in dental fees.

It is not the province of this or of any other journal to express an opinion as to whether dental fees are high or low; it is not for any person to express such an opinion. Any professional man may assess his services at a certain figure, and the members of the community may or may not come to him as it pleases them. The members of the medical profession charge certain fees to the general public; but when the public cannot pay these fees, they are charged what is known as an intermediate fee, which is within their means. People must be able to chew their food; if they cannot, they fall into ill-health. We have yet to learn that the dental profession has formulated a scale of fees that may reasonably be called intermediate. In the metropolitan areas matters are bad enough, though there are dental hospitals where the needier members of the community can receive attention. In the country, especially in New South Wales, the poor are in parlous plight. Some of them have carious teeth extracted, but they must remain edentulous. A man receiving the basic wage, and having a family of one or two children, cannot pay ten to twelve guineas for a set of teeth for his wife. He would like to pay something, and might even be able to pay

two or three guineas, but we can discover no arrangement by which he can do this. We know of no means by which he can get the work done unless he pays the full charge. Travelling dental clinics exist for school children; but if children who have left school become edentulous, they must remain edentulous. We are breeding in the country districts a race of edentulous adults, a state of affairs which is surely a disgrace to the community. Medical treatment is available for the poor and needy; surely some attempt can be made to provide dental treatment, at least for those who urgently require attention. If the State Governments will not take this matter up, it should be brought before the National Health and Medical Research Council; it is a matter of national health.

Current Comment.

THE ACTIVE AGENT IN "PRONTOSIL" THERAPY.

"PRONTOSIL" is now being used for all kinds of antiseptic and antistreptococcal purposes, quite remote from the original application upon which its reputation stands. It may therefore be well to remind ourselves that, *in vitro*, "Prontosil" has no bactericidal effect whatever. A slightly simpler but closely related substance, however, named sulphanilamide, or, if preferred, p-aminobenzenesulphonamide, has a directly inhibitory effect upon bacteria *in vitro*. A. T. Fuller asks therefore: "Is sulphonamide the active agent in 'Prontosil' therapy."[1]

"Prontosil" is active when given by injection or by mouth. Sulphanilamide is recoverable in significant amounts from the urine of patients treated by "Prontosil". Fuller has made estimations of the amount excreted by patients and mice, both normal and infected, who were given "Prontosil" of the same two varieties which Colebrook and Kenny praised so unstintingly in their now famous report from Queen Charlotte's Hospital. Estimations of "Prontosil" were made colorimetrically by comparison with standard solutions of the same pH. In the estimation of sulphanilamide, use was made of the diazo reaction for colour comparison. This is, of course, a group reaction not specific for sulphanilamide, but normal urine and blood filtrate do not give the reaction. Fuller's results show that up to 75% of the excreted "Prontosil" was in the reduced form of sulphanilamide. Thus one patient received 4·8 grammes of "Prontosil" by mouth in three days and 3·0 grammes by injection. A total of 0·8 gramme of "Prontosil" was recovered from the urine and the remainder had been reduced. The sulphanilamide appears in the urine in from four to six hours after the first dose of "Prontosil".

The mice experiments were interesting. In normal animals 35% of injected sulphanilamide and 49% of soluble "Prontosil" are not accounted for. Only small amounts were found in the body and the fæces. A part is without doubt completely destroyed. In infected animals the part destroyed is much larger. The infected groups receiving "Prontosil" excreted more sulphanilamide than did the normal group. Another finding of practical importance was that after injection smaller doses were more rapidly excreted than larger doses.

There is no doubt that more information is urgently needed as to the most suitable dose of "Prontosil", as to the best mode of its introduction, and as to its destination in the organism. If, as seems likely from Fuller's work, the derivative sulphanilamide is the active constituent of "Prontosil", future experimental and clinical research should be directed to this substance. Fuller wonders also whether a steady supply of sulphanilamide from a depot of "Prontosil" may not be more effective than the sudden flooding of the organism with a large volume of the simpler substance. On general grounds and by comparison with other substances of similar promise, such as "Salvarsan", it seems probable that an attempt at a *therapia magna sterilisans* by means of sufficient sulphanilamide would be worthy of trial.

[1] *The Lancet*, January 23, 1937.

THE CHEMICAL PROPHYLAXIS OF POLIOMYELITIS.

ALTHOUGH concentrated research has added greatly to our knowledge of poliomyelitis, the practical considerations of treatment and prevention have not so far been as well served as those of ætiology and epidemiology. Even the value of convalescent serum and of other biological methods of treatment is as yet doubtful, which means that no very effective treatment is at our command. The possibility of effective prophylaxis has been very much in the public eye lately, and it appears as if a simple and effective method may be available. The medical committee controlling the joint government and municipal campaign in Victoria recently expressed its opinion of the available methods. As they point out, general quarantine is impracticable, and the closure of schools is effective only if parents will isolate their children at home. The committee regards with some favour the possibility of conferring a passive immunity on contact children by the intramuscular injection of citrated blood taken from healthy adults, but it does not recommend the use of nasal sprays since their value is as yet doubtful. Certainly the results of previous efforts in this latter direction have not been encouraging, but the picric acid-alum spray previously tried has now been supplanted by a spray of zinc sulphate, which seems to be more promising. It will be remembered that chemical prophylaxis was also

tried during the influenza pandemic of some seventeen years ago, but the methods then employed were not productive of any striking results.

E. W. Schultz and L. P. Gebhardt have recently published an article summarizing the position with regard to the use of zinc sulphate.[1] These workers and many others have brought forward a number of important observations on poliomyelitis, and they now present the relevant facts as follows. Poliomyelitis is caused by a very small neurotropic virus which in monkeys, and probably also in man, reaches the central nervous system by way of the olfactory nerve. It is believed that the virus travels by axonal paths, which explains the disappointing results obtained from the use of immune serum in the experimental disease in monkeys, even though the serum is actually administered some days before the onset of symptoms. Consideration of the results of serum therapy in man also supports this belief. It would seem rational therefore to make some attempt to arrest the passage of the virus before it actually invades the protoplasmic substance of the neurones, and the only possible places where this might be done are the olfactory cells of the neurones which lie superficially in the olfactory mucosa, or the perineural spaces of the olfactory nerves. It is not positively known which of these two sites is the actual portal of entrance, but, as Schultz and Gebhardt remark, it is probable that the virus is not forced to pass a barrier of immune serum in order that it may reach the central nervous system. If this is true, it would follow that vaccines cannot be looked to as a trustworthy line of defence, for they can at best erect only such a humoral barrier which is, so to speak, wrongly placed, for the virus evades it by travelling by another route. At this point it is interesting to ask to what acquired active immunity is due. It may depend upon some intimate alteration in the cells at the portal of entry, a logical concept, for where there is local susceptibility there may surely also be local resistance. This view would regard the humoral defence against the virus as largely adventitious. Is it possible then either to enhance the local resistance of the olfactory cells and other tissues or to find some successful chemical method of protection? Numbers of chemical substances have been used experimentally, including alum, tannic acid, picric acid, mercurochrome *et cetera*, and a certain definite measure of success could be obtained with all. The most surprising feature of this work is specially commented upon by Schultz and Gebhardt, that is, the remarkably long persistence of the protection thus afforded the animals used for experiment, especially with certain of the agents used. Forty various chemicals have been used by the authors in their work, but the most promising appears to be zinc sulphate, which is simple, cheap and effective, and of low toxicity. Two or three successive daily intranasal sprays with a 1% solution of zinc sulphate in 0·9% saline solution have been effective in protecting nearly all of a large series of animals from infection of virus administered by the intranasal route. The doses of virus used were sufficient to cause symptoms of disease in 90% of the controls. The degree of protection is so remarkable, according to these experiments, that the authors strongly favour the extension of investigation to man. They rightly stress the word "investigation" because it cannot be taken as certain that the results obtained in monkeys will apply to man, and they maintain that the application of such a prophylactic measure as this should be in competent and well-trained hands. Further, the results must be adequately controlled, which is a most difficult matter in actual field work when dealing with the general public. Schultz and Gebhardt advise that the solution containing 1% zinc sulphate in saline solution with the addition of a local anæsthetic should be applied once every fortnight when the risk of infection is great, or even preferably on two or three successive days and thereafter once every two weeks. The addition of some local anæsthetic ("Pontocaine" is used by the authors) is advised on account of the local pain which the zinc solution often causes. Some headache and local discomfort ensue for a few hours after the application, but careful observations of any possible side effects should be made, though no harmful results have been observed in animals.

The actual technique of the application is very important. M. M. Peet, D. H. Echols and H. J. Richter contribute an article to the same journal on this subject. They advise a solution of 1% zinc sulphate and 1% "Pontocaine" hydrochloride in 0·5% sodium chloride, which is nearly isotonic and which appears to be comfortable and non-toxic in action. A point of some importance is the possibility of functional damage to the olfactory mucosa, causing impairment of the sense of smell. These authors carried out a series of investigations on healthy students and found that although the sense of smell is impaired or lost for a time, it returns to normal within a couple of weeks. The real difficulty lies in reaching the correct area with the spray, and perversely enough this is easier to do in a monkey than in a child. An ordinary atomizer is useless, as the spray does not go above the middle turbinate bone, and it is believed by the authors that the disappointing results obtained by chemical sprays heretofore have been due to an incorrect technical method. It is necessary to use a fine long tip on the atomizer and to introduce it by direct vision past the middle turbinate. One cubic centimetre of the solution is introduced and the process is repeated in the opposite nostril. A successful spraying should cause loss of olfactory sense. It is obvious that this method must be applied by a skilled staff, and haphazard methods would be likely to do a disservice to a scheme of prophylaxis which would appear to be of definite promise. It is hoped that any work done along these lines in Australia, whether by corporate bodies or individuals, will be carried out under standard conditions and will follow a recognized technique.

[1] *The Journal of the American Medical Association*, June 26, 1937.

Abstracts from Current Medical Literature.

GYNÆCOLOGY.

Effect of Mumps on the Female Genitalia.

H. BOSCH (*Monatsschrift für Geburtshülfe und Gynäkologie*, December, 1936) considers that in many cases of scanty menstruation and sterility the possibility of the effect of mumps may be overlooked. Though evidence of pathological changes in the ovaries is scanty, it is fair to assume that similar changes to those in the testicles may occur. By sclerosis of the outer covering of the ovary maturation of the follicles is hindered, and this change may also interfere with the action of hormonal remedies. The author considers that the effects of mumps on the pituitary should also be considered as a causal factor. Therefore he advocates a close inquiry into any history of lower abdominal pain in young girls, as it may be the only symptom of effects of mumps.

Treatment of Chronic Parametritis.

K. LOGOTHETOPOULOS (*Monatsschrift für Geburtshülfe und Gynäkologie*, February, 1937) advocates the treatment of massive parametritis by the formation of a fixation abscess. He injects five to six cubic centimetres of turpentine oil *per vaginam* into the infiltrated area. The injection is followed by a rise of temperature and pain which will require the use of sedatives. Usually the abscess which forms is opened about forty-eight hours after the injection. The cavity is explored with the finger, as much *débris* as possible is removed, and gauze drainage is established. The results in seven cases so treated were excellent, and in a few weeks the infiltrated area disappeared with general improvement of the patient's condition.

The Treatment of "Broad Ligament Neuritis" by "A.B.A."

ARTHUR M. SUTHERLAND (*Journal of Obstetrics and Gynæcology of the British Empire*, April, 1937) reports the result of his treatment of "broad ligament neuritis" by the preparation known as "A.B.A." The syndrome associated with broad ligament neuritis is given as constant pain in one or both sides of the lower part of the abdomen, sometimes extending to the back, but down one or both sides. This pain is accentuated during the pre-menstrual period, the left side is more frequently affected than the right, and the pain is aggravated when the cervix is forcibly pushed to one side or the other. On examination the cervix is found to be more or less fixed at the vaginal vault; sometimes it is drawn to one side or the other. The condition is almost invariably a sequel to childbirth. Chronic cervicitis is usually present. The author reports a series of 52 consecutive patients suffering from chronic pelvic pain in whom this syndrome was present. In 39 the pain was on the left side, in seven it was on the right side, and in six it was bilateral. The preparation "A.B.A." is put up as a local anæsthetic and was originally recommended by Gabriel for the treatment of *pruritus ani*. General anæsthesia is used. The preparation is injected with a 10 cubic centimetre "Record" syringe, with a long fine needle, into the base of the broad ligament. Dosage is four cubic centimetres, although up to six and ten cubic centimetres have been used without ill-effect. Complete cure was claimed in 25 cases, partial benefit in 21, no improvement in four cases, and two patients could not be traced. Injection is given through the vaginal wall. The author claims that this treatment saves operation in a number of cases.

Treatment of Menorrhagia.

J. J. SSARYGIN (*Monatsschrift für Geburtshülfe und Gynäkologie*, March, 1937) discusses the treatment of stubborn cases of menorrhagia by means of hot packs applied to the breasts. When the period starts, hot saline solution compresses, commencing at a temperature of 38° C. and gradually increased to 42° C., are applied. Each application lasts for ten to twelve minutes, and the period of time is gradually increased to a quarter of an hour. On an average two to five applications are required. The effect is produced apparently by the stimulation of the vegetative nervous system. There are no contraindications, even if pelvic complications are present. The effect is obtained in a shorter time by the use of saline solutions rather than those of plain water.

Clinical Uses of the Female Sex Hormone.

C. KAUFMANN (*Journal of Obstetrics and Gynæcology of the British Empire*, April, 1937) reports on his experiences in the use of the female sex hormone. The follicular hormone is responsible for proliferation of the genitalia and exercises a profound effect on the whole body. The *corpus luteum* hormone is responsible for the preparation of the uterus for pregnancy and for the maintenance of pregnancy. Sufficient information is not yet available in regard to any extragenital effect of the *corpus luteum* hormone. When hormones are used for treatment it is important to employ the correct dosage. The author points out that the dosage has increased tremendously of recent years, both as the result of finding fresh sources of supply and as the result of experience. In primary amenorrhœa he finds that the ovarian hormones are useless in an attempt to maintain a spontaneous menstrual cycle after the cessation of treatment; but patients suffering from general symptoms of deficiency can be cured with the use of follicular hormone. In secondary amenorrhœa the first essential is to make a most complete and thorough examination in order to exclude any extragenital condition capable of causing amenorrhœa, such as pulmonary tuberculosis and other general causes. The results of treatment in secondary amenorrhœa are on the whole poor. The author gives his dosage for various conditions. The treatment that gave success in some cases was a transfusion of from 250 to 300 cubic centimetres of blood from a pregnant woman. This gave striking results in half the author's cases. In dysmenorrhœa in young women with an acutely anteflexed uterus the author claims that the symptoms can be entirely removed with follicular hormone in comparatively small doses. In sterility he claims good results for the use of hormone, particularly the follicular hormone. In scanty menstruation good results follow the use of follicular hormone. The juvenile hæmorrhage or menorrhagia of puberty can be stopped by means of the hormone of the *corpus luteum*. In preclimacteric hæmorrhages it is necessary to exclude carefully the presence of malignant growths; after this has been done the *corpus luteum* hormone is of use. It is also of great use in cases of habitual abortion. The author claims successful results in the treatment of general disturbances at the climacteric. The dosage and method of use of the various preparations are given in detail.

Pseudo-Menstruation in the Human Female.

CHARLES MAZER, LEON ISRAEL AND LEON KACHER (*Surgery, Gynecology and Obstetrics*, July, 1935) undertook a study of the effect of the two ovarian hormones, œstrin and progestin, on the mucous membrane of the uterus. They are of the opinion that there is a condition, called by them pseudo-menstruation, which is clinically indistinguishable from the normal menstruation, but which arises from an endometrium totally lacking the secretory (progestin) phase. By a comparative study of endometrial tissues obtained by curettage before menstruation from 68 regularly menstruating fertile women, they have come to the conclusion that pseudo-menstruation is rarely encountered in fertile or potentially fertile women. Three independent factors may produce pseudo-menstruation, namely, failure of ovulation (anovulatory menstruation), inherent or acquired lack of uterine responsiveness, or a quantitative disparity in production of the two ovarian hormones. When there was failure of ovulation and luteinization they found endometrial hyperplasia. Pseudo-menstruation is clinically indistinguishable from the normal type of menstruation, because the rhythm and duration of the bleeding are basically normal. If there is a developmental or acquired

uterine defect which prevents the organ from responding to the normal ovarian activity, there is premenstrual atrophy of the endometrium, despite the presence of a normal level of œstrogenic substance in the blood and urine. If, however, there is a qualitative or quantitative disharmony between the two ovarian hormones, there result an inadequate preparation of the endometrium and suppression of the premenstrual phase. The article is well illustrated with histological specimens. The authors have found that cyclic uterine bleeding, which is clinically indistinguishable from normal menstruation, from an endometrium totally lacking the usual secretory changes, occurs in 30% of sterile women who present no abnormality.

OBSTETRICS.

Visscher-Bowman Pregnancy Test.

B. FRIEDRICH (*Monatsschrift für Geburtshülfe und Gynäkologie*, October, 1936) states that while the Aschheim-Zondek reaction has apparently superseded all previous attempts to establish a chemical test for the early diagnosis of pregnancy, that of Visscher-Bowman promises much of value. To one cubic centimetre of urine is added one drop of 0·5% hydrogen peroxide, five drops of a 1% solution of phenylhydrazine hydrochloride, five drops of a 5% watery solution of methyl cyanide and five drops of concentrated hydrochloric acid. The mixture is heated for twenty-five minutes in a water bath. A positive reaction consists in a reddish-brown coloration associated with a flocculent deposit. The reaction is "negative" if the colour is straw-yellow associated with no deposit or a dense deposit. The author points out that morning urine gives the best results. It must be free from any albumin and the specific gravity must not be above 1015. If it be above this figure, the urine is diluted down to this figure with distilled water. The reagents must also be fresh—the phenylhydrazine not more than two days and the hydrogen peroxide and methyl cyanide not more than eight days old. The author's results correspond with those of Visscher-Bowman, namely, 90% to 93% positive. The reaction is apparently due to a colour reaction between prolan in the urine and hydrochloric acid.

Diabetes Complicating Pregnancy.

PRISCILLA WHITE (*American Journal of Obstetrics and Gynecology*, March, 1937) analyses the results of 271 pregnancies which occurred in 191 diabetic women who consulted Dr. Joslin between 1898 and October, 1935; approximately half occurred in the pre-insulin era. With the introduction of insulin there is a drop from 29% to 25% in the stillbirth rate, and from 27% to 16% in the miscarriage rate. Early abortion and miscarriage are attributed to lack of control of the diabetes and endocrine disturbance. Stillbirth is probably due to the imbalance between prolan and œstrin, and not to over-nutrition, since there has been very little alteration since the introduction of insulin. For years the literature on obstetrics and diabetes has contained accounts of the frequency with which an over-developed, macerated fœtus has been born to the diabetic mother; but this is not an unfailing characteristic of diabetes. Prolan is a substance capable of producing giantism. Smith and Smith have shown that there is an increase in prolan in those patients who are doomed to produce abnormal children. The treatment of the diabetes during pregnancy will vary with the problems of the individual patient. The author discusses the treatment that should be adopted in different stages of pregnancy.

Incidence of Pregnancy Following Sterility.

H. J. FREYSCHMIDT (*Monatsschrift für Geburtshülfe und Gynäkologie*, December, 1936) summarizes the histories of 102 cases of sterility which were thoroughly investigated in his clinic. After treatment, mainly by tubal insufflation and correction of displacements, he endeavoured to follow up the patients as regards subsequent pregnancies. Forty-nine patients replied to the *questionnaire*, and in seven instances only had pregnancy taken place. The author considered that in four of these the occurrence of pregnancy could be attributed to the previous treatment. Pregnancy was noted most frequently in cases in which retroflexion had been a prominent symptom. Only one patient in ten with hypoplasia subsequently became pregnant, while only 6% of the patients with partially closed tubes which were dilated by insufflation had a later pregnancy. The author emphasizes the need for careful examination of each patient in order to choose the best method of treatment, and he considers that hormonal therapy is likely to be of considerable assistance.

Analgesia in Labour.

GERTRUDE NIELSEN (*American Journal of Obstetrics and Gynecology*, February, 1937) discusses the advantages of a minimum amount of anæsthesia and the benefit obtained by educating the patient along sound ideas of child-bearing. The discovery of forceps led to their general use in France, whilst in England the transformation of a natural process into an artificial one was resented. There appears to be a very strong tendency today to return to the French school, and the author is of the opinion (which she shares with many observers) that a major cause of this change is the increased use of narcotics. This contention is borne out by a study of foreign statistics. In Holland and the Scandinavian countries, which have the lowest infant and maternal mortality, analgesics are used judiciously, and operative delivery is resorted to in only 3%, as compared with 20% in New York. The perfect analgesic has yet to be found. Religion and folklore, as well as early obstetric practices, have produced in civilized women a fear of child-birth which, if not overcome by proper psychological management, constitutes a serious obstacle to normal parturition. Much damage is done by irresponsible allusions to the dangers of child-birth and by sensational magazine articles.

The Diagnostic Value of X Rays in Placenta Prævia.

S. C. HALL AND J. F. LYNCH (*American Journal of Obstetrics and Gynecology*, April, 1937) investigated at Saint Mary's Hospital a series of patients with bleeding, and they found that in uterine hæmorrhage occurring in the last trimester of pregnancy X ray studies are useful aids to diagnosis and treatment. The technique was to inject 20 cubic centimetres of "Skiodan" intravenously, after which an X ray film was made. This technique is different from that of the other investigators who instilled 40 cubic centimetres of 12% sodium iodide solution into the bladder and then took a direct antero-posterior X ray picture of the abdomen. Diagnosis in earlier cases is made by finding a space between the presenting part and the bladder of more than one centimetre. In a normal pregnancy the head causes an indentation of the bladder resembling a half moon; whereas with low implantation of the placenta half of the moon is more to the right or left, and the distance is greater from the presenting part of the bladder than one centimetre.

Intraabdominal Hæmorrhage During Labour.

H. SELBACHER AND T. KERNAU (*Monatsschrift für Geburtshülfe und Gynäkologie*, January, 1937) have summarized the literature concerning intraabdominal hæmorrhage from rupture of varicose veins in the broad ligament, and describe a fatal case occurring in a young *primipara*. The majority of cases occur in women about thirty years of age who are in labour. All patients complained of acute sudden pain. The subsequent progress was either the rapid onset of symptoms of blood loss or a slower development which resembled peritonitis in its features. In the acute variety operation was generally performed at once and there was a higher rate of recovery. The authors emphasize the statement that in the presence of progressive anæmia and a poor pulse a diagnosis of ruptured varix must be considered. An exploratory puncture of the pouch of Douglas may lead to mistakes if a varicose vein is entered. The usual treatment is laparotomy with Cæsarean section and ligature of the bleeding veins.

British Medical Association News.

ANNUAL MEETING.

THE annual meeting of the Western Australian Branch of the British Medical Association was held at the Hospital for the Insane, Claremont, on March 21, 1937, DR. A. SYME JOHNSON, the President, in the chair.

Financial Statement.

Consideration of the Treasurer's report and balance sheet was deferred to the next meeting. As the report was subsequently adopted, it is published herewith.

Dr. T. C. Boyd and Dr. A. W. Farmer were elected Honorary Auditors.

Annual Report of Council.

Dr. A. Syme Johnson then read the annual report of the Council. The report is as follows.

I have pleasure in presenting the report of your Council for the year ending March, 1937, as follows:

Membership.

Membership of the Branch has increased from 268 to 271.

Deaths.

I regret to report that since the last annual meeting we have lost Dr. D. W. H. Mackie, of Narrogin, who has been a member of this Branch for many years.

Meetings.

There were ten general meetings held during the year, with an average attendance of 36 members. This is a slight improvement on the attendance for the previous year (31), but, considering the metropolitan members are over 150 in number, I do urge members to urge their colleagues to increase the number of attendances at meetings. A great deal of trouble is taken for the preparation of useful work for these meetings, and it is regrettable it is not more appreciated.

The annual general meeting was again held, by the kind invitation of Dr. Bentley, at the Hospital for Insane, Claremont.

A clinical meeting was held at the Perth Hospital by the kind arrangement of Dr. Trethowan; also a clinical meeting at the Fremantle Hospital by the kind arrangement of Dr. Day-Lewis.

A joint meeting was held between this Association and the Odontological Society, when the interesting subject of "Pyorrhœa" was discussed, there being present 24 doctors and 27 dentists.

A special meeting was held in conjunction with the Federal Health Council.

A general meeting was held during Post-Graduate Week, when interesting papers were read by Dr. S. O. Cowen and Mr. W. A. Hailes.

The first meeting ever held outside the metropolitan area was held during the year at Northam, there being 40 members attending.

Interesting papers were read during the year by Dr. Nattrass, Dr. Carter, Dr. McWhae, Dr. Male, Dr. Aberdeen, Dr. Lovegrove, Dr. Hodby.

The annual dinner was held this year at the Adelphi Hotel, and I am glad to report that the number at the dinner was 73, compared with 43 last year.

Council Meetings.

The Council met 12 times, with an average attendance of 9, the individual attendances being as follows:

Dr. Atkinson	3	Dr. Le Souef	10
Dr. Carter	11	Dr. Moss	10
Dr. F. Gill	10	Dr. Paton	6
Dr. Hayward	12	Dr. D. Smith	10
Dr. Syme Johnson ..	12		

Owing to the increased volume of work of the Council, the Council decided that an additional member should be appointed, making the number of councillors elected from three to four. This was duly presented to a special meeting and the action of the Council confirmed.

President-Elect.

The Council with much regret has to report that Dr. Paton found it necessary to relinquish this position, and has, in accordance with the regulations, appointed Dr. F. W. Carter as President-Elect, and appointed Dr. H. Stewart to fill the vacancy on the Council.

Mines Medical Fund Agreement, Kalgoorlie and Boulder.

I am glad to report that an agreement was reached between your Council and the Chamber of Mines, by which the doctors at Kalgoorlie-Boulder receive an additional 1s. 6d. per day for each mine worker on their lists. I will not labour the history of this case, but desire to state that Kalgoorlie-Boulder is the only portion of the State where the *Workers' Compensation Act* does not exist as far as mine workers are concerned. The Government would not agree to the alteration of the agreement by which the mines collected from the miners 3s. per pay, which is paid to the doctor on whose list the miner is, and for which the doctor gives professional services as well as paying for hospital treatment. It was agreed by the Chamber of Mines, however, that they would pay the additional 1s. 6d. per pay per miner in lieu of the *Workers' Compensation Act*, as there would be a great likelihood of dislocation of the industry if the *Workers' Compensation Act* was insisted upon. This agreement is for ten years.

Standard Mining Agreement in Other Districts.

A Standard Mining Agreement was prepared in 1936 and submitted to various doctors and mines medical funds outside Kalgoorlie and Boulder, and as various objections were raised the matter was again referred back for legal advice, and was submitted to and approved of by special general meeting in January, 1937, and it is hoped that this agreement will now be signed by all doctors and medical funds in the other mining centres.

Workers' Compensation Boards.

Your Council has represented to the Government Actuary improvements for holding these Boards, both for procedure and accommodation, and trusts that benefit will accrue.

Broadcasting.

Interesting broadcasting of a popular nature on medical topics by members of the Branch has been carried out during the year. I would ask members to take an interest in this matter and advise their willingness to broadcast and suggest material for broadcasting.

Scale of Fees to be Charged in Community Hospitals.

This matter was considered by several meetings of the Hospital Policy Subcommittee and the Council, and also by general meeting, and the matter was finalized and passed in August, 1936, advising of reasonable fees to charge, this schedule being subject to review at the end of twelve months or when deemed necessary.

Workers' Compensation Act.

A general meeting approved of the alteration of Certificate "A" under the Amended Schedule Number 2. This certificate is a little more elaborate, but very easy to fill in, and should be a benefit to all concerned.

Post-Graduate Week.

A very successful week was held in October, 1936, the visiting lecturers being Dr. S. O. Cowen and Mr. W. A. Hailes. As a result of the meeting with delegates from districts' associations, a request has been forwarded to the Post-Graduate Committee to hold the next post-graduate course in winter, when locums should be more available.

Statement of Receipts and Payments for Year ended December 31, 1936.

RECEIPTS.	£ s. d.	£ s. d.
December 31, 1935—		
Bank of New South Wales, Current Account		299 5 10
Cash on Hand		51 0 0
Interest—		
From Commonwealth Bonds	98 10 6	
Australasian Medical Publishing Co. Ltd.—Debentures	15 5 0	
Fixed Deposit (N.S.W.)	12 0 0	
		125 15 6
Fixed Deposit, paid January, 1936		200 0 0
Annual Subscriptions		970 10 6
Anatomy School	12 12 0	
Honorary Staff, Perth Hospital, Gift to Library	10 0 0	
Western Australian Clinical Reports	1 0 0	
British Medical Association Dinner, 1936	51 0 0	
		74 12 0
Collected for Benevolent Fund		84 0 0
		£1,805 3 10

PAYMENTS.	£ s. d.	£ s. d.
Printing	47 0 2	
Postages and Telegrams, *et cetera*	68 11 9	
		115 11 11
Assistant Secretary's Salary (including Office Fee and Clerical Assistance)		150 0 0
Salary, Honorary Treasurer's Assistant		10 0 0
London Account, Cost Journals		353 13 3
Sydney Account, Cost Journals		281 0 0
Legal Expenses		9 19 6
Railway Fares, Delegates Kalgoorlie		22 17 6
Contribution to Federal Council		24 10 0
Anatomy School		12 3 11
Dinner Fund		77 17 9
Library Account		109 0 4
Paid to Medical Benevolent Fund		84 0 0
		1,250 14 2
December 31, 1936—		
Cash on Hand		14 14 0
Bank Account, Bank New South Wales, Perth		539 15 8
		£1,805 3 10

Invested Funds Account.

	£ s. d.	£ s. d.
December 31, 1935.		
Invested Funds on Hand—		
Commonwealth Bonds	2,510 0 0	
F.D.R., Bank of New South Wales	200 0 0	
Australasian Medical Publishing Co. Ltd.	345 0 0	
	£3,055 0 0	
January 21, 1936.		
Fixed Deposit paid off to Current Account		200 0 0
Invested Funds on Hand, *per* Bank Certificate, at December 31, 1936—		
Commonwealth Bonds	£2,510 0 0	
Australasian Medical Publishing Co. Ltd.	£345 0 0	
		2,855 0 0
		£3,055 0 0

We hereby certify that this Statement has been audited according to the books and vouchers submitted and found correct.

(Sgd.) T. C. BOYD, Honorary Auditor.
(Sgd.) A. W. FARMER, Honorary Auditor.
(Sgd.) DONALD SMITH, Honorary Treasurer.
February 15, 1937.

and when the meeting will not interfere with country members attending local districts' agricultural shows, which apparently was the case last year.

Recruitment of Members of the Medical Profession.

This matter has been given close attention by the Council, and the Federal Council has been communicated with to draw up a uniform scheme for the protection of medical practices of members in the event of their being called up for active service.

Protection of Persons against Gas Attacks.

Dr. McWhae read a most interesting paper, and also gave a practical demonstration to members of the use of gas masks.

Immunization against Diphtheria.

At the instigation of the honorary staff of the Children's Hospital this matter has been given careful attention by your Council, and all medical officers of health throughout the State have been requested, with the cooperation of their colleagues, to urge local health authorities to do all in their power to carry out immunization.

Uniform Medical Registration Throughout Australia.

This matter has been considered and submitted to the Federal Council, together with Dr. Paton's report. While your Council is not in favour of uniform medical registration, it is in favour of Federal Government control.

Special Medical Committee.

I desire to express the great appreciation of the Council of the service of the Special Medical Committee, comprising Dr. Moss, Dr. F. Gill and Dr. Aberdeen. Very excellent work with the underwriters has been done by this committee, and, generally speaking, members have loyally agreed to the decisions of the committee.

There were several other matters of less importance considered and dealt with by the Council.

Office-Bearers for the Year.

Office-bearers for the year were sufficient to fill all positions and therefore no ballot was necessary. I declare the following elected:

President: Dr. F. W. Carter.
President-Elect: Dr. L. A. Hayward.
Ex-President: Dr. A. Syme Johnson.
Honorary Treasurer: Dr. D. Smith.
Honorary Secretary: Dr. L. E. Le Souef.
Four Members of Council: Dr. N. Cuthbert, Dr. F. Gill, Dr. M. Moss, Dr. H. H. Stewart.

I would like to thank the members of the Association for the support they have given to me as President. I especially desire to thank Members of Council, the Honorary Secretary and Honorary Treasurer for their loyal support during the year.

Induction of President.

Dr. A. Syme Johnson then introduced Dr. F. W. Carter, the President for the ensuing twelve months, and wished him a successful term of office.

SCIENTIFIC.

A MEETING of the Victorian Branch of the British Medical Association was held at Mooroopna Hospital, Mooroopna, on May 29, 1937, DR. J. P. MAJOR, Senior Vice-President, in the chair. Part of the meeting took the form of a series of demonstrations by the members of the honorary medical staff of the hospital. The discussion on diverticulosis and diverticulitis following the reading of a paper by Dr. J. A. Kennedy was published in the issue of August 14, 1937.

Hypoglycæmia.

DR. ANNIE BENNETT showed a male patient, thirty-four years of age, whose chief complaint was that he felt weak in the legs and arms, and that even when he wakened his muscles felt tired; the tired feeling was worse after slight exertion and from boyhood he had preferred to lie down and to read rather than to join in with the outside interests and games of his comrades. The condition had become worse in the previous three years, and, whereas he had previously had a good appetite, latterly his appetite had been poor; he did not take any alcohol and had always had an aversion to fat in food; latterly even the sight of fatty food had spoilt his meal. Frequency of micturition had always been present and he had often noticed transient frontal headache and blurring of vision when he stooped. He was tall and thin, and usually weighed about eleven and a half stone. He had had only one real illness, which had been cured by the removal of the appendix after about a year of attacks of pain in the right iliac fossa. At times he had a slight cough with discharge of mucus from the back of the nose and throat.

Dr. Bennett saw the patient first in December, 1936, when his appearance was much the same as it was at the time of the meeting; she had noticed the brownish tinge of the skin, the furred tongue and his general flabbiness and sluggish reflexes. The systolic blood pressure was 140, the diastolic 90 millimetres of mercury. The specific gravity of the urine was 1020 and no albumin or sugar was found in it. The serum failed to react to the Wassermann test. On January 27, 1937, a sugar tolerance test was made. The fasting blood sugar content was 0·082%, and after the usual intake of fifty grammes of glucose by mouth the blood was examined at hourly intervals and found to contain 0·065, 0·085, 0·075 and 0·075 *per centum* of sugar. The patient worked at the local fruit cannery and felt better while taking thyreoid gland tablets. Dr. Bennett found that the suitable amount was one grain (fresh gland) three times a day. Another blood sugar examination was carried out five days before the meeting. The fasting blood sugar content was 0·070 *per centum*. This time the estimations were made at half-hourly intervals after the giving of fifty grammes of glucose by mouth, and the findings were 0·099, 0·082 and 0·070 *per centum*. After a test meal no free hydrochloric acid was detected in the stomach and the total acidity was 6. The patient was still taking the same amount of thyreoid gland.

DR. L. E. HURLEY commented on the fact that the fasting blood sugar was practically normal and that the readings were actually lower after the glucose. These findings were not unusual, and he remembered that Professor Barr had pointed out that by giving large doses of glucose at times these patients would be made worse. The theory of this effect was that the glucose served to stimulate an over-production of insulin. In treatment it was better often to use a high-fat, high-protein diet. The weakness had to be ascribed to a low blood sugar content.

DR. ERIC COOPER said that he could not help Dr. Bennett concerning the ætiology of the condition. He had usually failed to get the patients to take a high-fat diet, but had been more successful in getting them to have more frequent meals, say six a day. When they had reduced weight by means of thyreoid gland tablets they took the fat better and were no longer hypoglycæmic. It was by no means unusual to see the fall in the blood sugar after glucose or after a meal was taken. The ketogenic diet after the style of that used for epilepsy was effective if the patient could be persuaded to take it.

Dr. Bennett thanked Dr. Hurley and Dr. Cooper, and stated that she hoped to be more successful with the dieting, now that she knew that the gastric acidity was so low; if she administered dilute hydrochloric acid, she expected that the patient's appetite would be improved.

Osteomyelitis of the Femur.

DR. REGINALD MILLS showed a boy, three years of age, who had been admitted to hospital in September, 1936, after an illness of four days, during which he had been starting in his sleep; he had feverishness and anorexia associated with pain in the left hip and limp of the left leg. The boy's temperature at the time of his admission to hospital was in the neighbourhood of 41·1° C. (106° F.). The left thigh was flexed and everted and all the movements at the hip joint were limited. Two hours after his admission to hospital a convulsion occurred. Tenderness was present over the great trochanter and there was a small range of painless movement at the hip joint. There was nothing of importance in the past history. Three weeks before the onset of this illness the boy had had a common cold with some pain in the right ear; this had cleared up completely.

At the operation Dr. Mills trephined the femur and obtained pus from near the lower part of the trochanter and down the shaft for about three inches, but before reaching the centre of the shaft he had got beyond the pus-yielding region. The trephine holes were left open and the wound was packed loosely and a plaster spica was applied. The patient was very ill for ten to fourteen days, but the temperature gradually subsided and was normal within three weeks of the operation; he had very little pain throughout the illness. The plaster had been changed periodically, as the soakage spoilt it, and at the time of changing the plaster it was seen that the wound was granulating satisfactorily and good progress was being made. The plaster had been dispensed with and there was very little disability; the boy could walk quite well on the affected leg. Apart from intercurrent tonsillitis and the presence of a small boil on the buttock, convalescence had been uneventful. Dr. Mills asked whether it was not unusual to find osteomyelitis limited to the greater trochanter and not extending right along the shaft, beyond the centre at least.

DR. VICTOR HURLEY said that in acute osteomyelitis the degree of rise in temperature and amount of constitutional disturbance were out of proportion to the extent of bone involved. With reference to treatment, there had been a swinging backwards and forwards of opinion as to the amount of operative interference necessary, from leaving the patients at rest to treating them radically. Dr. Hurley considered it rational to provide drainage, as Dr. Mills had done, and not to proceed to extensive tunnelling.

DR. C. J. O. BROWN drew attention to the great importance of fixation of the affected limb at rest. This was the principle of the method that had been advocated by Dr. Fay Maclure. Dr. Mills deserved congratulation, and the successful result was largely due to the immobilization of the whole limb in plaster, which had prevented the massaging of the products of infection into the system.

DR. F. KINGSLEY NORRIS stated that the mildest of upper respiratory infections occurring at the age of this patient was dangerous, owing to the patient's small ability to localize any infection. It was quite reasonable to suppose that the sequence of events in this case had been that the bone focus followed on septicæmia which had been caused by the upper respiratory infection. The important thing in the management was the fixation of the limb at rest; the joint usually escaped and the disease remained extra-articular.

DR. PAUL JONES said that in osteomyelitis he found that the hardest part was to determine when to operate. In his experience, if pus was not found immediately at operation, the discharge of pus continued for a long time.

Suppurative Arthritis of the Hip Joint with Dislocation.

DR. W. L. ARMSTRONG showed a boy, fifteen years of age, who had come under treatment on September 5, 1936, with the history that after moderate exertion he had felt pain, definitely localized to the middle third of the right femur, but there was no tenderness or limitation of movement at the hip joint. No abnormality could be detected in the pelvis or hip joint, even in a skiagram, though the boy's temperature was 38·3° C. (101° F.). Twenty-four hours later, on account of complaint of pain at the left lateral border of the sacrum, Dr. Armstrong operated through an incision over the sacro-iliac region and inserted a needle into the hip joint, but obtained no evidence as to the situation of the focus. Toxæmia became pronounced and the fever was high; but there was still lack of evidence of the position of the focus; and Dr. Armstrong explored the outer table of the ilium and inserted a needle into the hip joint, again fruitlessly. As the temperature was still high and the patient's general condition became worse, Dr. Armstrong explored the hip joint and found pus in it and a focus in the acetabular centre. At the time pain and limitation of movement at the hip joint were still absent. The limb was put up in extension, but spontaneous dislocation occurred. The patient was able to walk quite well at the time of the meeting, though he used a stick, owing to lack of confidence.

Dr. Armstrong said that he wished to draw attention to the small extent of the focus and to the absence of evidence as to the site of the lesion, though the general disturbance was extremely severe.

DR. THOMAS KING said that he considered the management of this case had been very good indeed, but he did not think that it was very unusual to have quiet suppurating arthritis of this type. It was not infrequently seen in elderly patients who might have a bony ankylosis without a clear history of the original damage. At present the boy had good function in a false hip joint, but it had to be realized that in the course of time the function would become worse. The patient had told Dr. King that he had walked two miles on the previous day without undue distress. The low Schanz or Lorenz osteotomy might have to be considered later on.

DR. W. A. HAILES discussed the future of the patient with a false joint and adducted leg. He would like Dr. King to say what the amount of shortening in the limb was at present, and how much he thought it could be lessened later by dividing the femur. In another case with two inches of shortening the surgeon had shortened the sound limb and the patient got a perfect functional result. The amount of shortening was the only disability in these cases, but it was gambling with the sound limb to shorten it, though it should be possible to shorten it successfully in a young patient such as the boy shown by Dr. Armstrong.

Dr. King, in reply to Dr. Hailes, said that he had measured the boy's legs and at present the amount of shortening was one and a half inches; but he thought that in time he would become very lame and that the shortening would increase to about three inches. Dr. King demonstrated by means of diagrams that the pelvis would tilt towards the affected side, lengthening the sound leg and shortening the affected leg, so that the patient could overcome the adduction and obtain extra support from two-point contact with the pelvis. By means of a low osteotomy the second point of contact could be obtained without the tilt on the pelvis and the legs could be brought parallel, overcoming the adduction. This procedure would still leave the patient with some shortening. It was far more serious to undertake the shortening of the sound leg than to carry out the Schanz osteotomy, and he would advise a very low osteotomy at a later date.

Dr. Hailes said that he would undertake shortening of the sound femur with fear and trembling.

DR. VICTOR HURLEY said that on comparing the films it looked as if the boy was correcting the adduction himself, and the problem seemed to be more one of correcting the shortening alone. In the film ankylosis appeared to be present, but there was no question that the boy had a range of movement. It was unwise to draw conclusions about ankylosis from the film when there were no trabeculæ passing across the site of contact.

Dr. Armstrong thanked those who had contributed to the discussion, and emphasized the difficulty that had arisen in this case because there had been so few localizing signs and symptoms, and even those present had been referred to the middle third of the femur; the only tenderness and pain had been limited to an area the size of half a crown on the side of the sacrum. Dr. Armstrong had opened the hip joint only after considering other possible procedures and finding them inadvisable.

Sympathectomy for Ulceration.

Dr. Armstrong showed another patient, a single woman, forty-five years of age, who, at the age of thirty-seven years, had come under notice with areas of solid œdema associated with pain and spasticity and multiple ulcerated patches affecting the right arm and leg and side of the body. In 1930 Dr. Armstrong had done a sympathectomy operation on the femoral artery in Hunter's canal. In both limbs the areas had been remote from the extremities and the hands and feet had remained unaffected; the œdematous patches had a dead, icy feeling about them; the knee jerks gave a spastic response and hyperextension of the big toe had occurred. Nine months before the meeting Dr. Armstrong removed the patient's tonsils and carried out a cervical sympathectomy, and in March, 1937, he performed lumbar sympathectomy. The patient was able to straighten the knee, and his condition had improved. In contrast, Dr. Armstrong recounted briefly the history of a woman, thirty-one years of age, in whom the terminal parts were affected. A gangrenous finger was amputated, and later, when the fourth finger became infected, Dr. Coates performed cervical sympathectomy, which had been followed by a disappearance of the symptoms and a lessening of spasticity, with increased warmth and colour.

DR. L. E. HURLEY said that he wondered whether the patient shown by Dr. Armstrong was suffering from scleroderma. There was no pitting œdema, and with elevation and dependency of the affected limbs some change of colour could be detected, so that probably some organic cause was present. If three signs were considered, it was possible to separate the three main conditions to be considered in the diagnosis. The three signs were thickening of the skin, ulceration not affecting the terminal portion, and organic vascular obstruction and not spasmodic obstruction. In Raynaud's disease trophic phenomena occurred with thickening of the skin; in *thrombo-angiitis obliterans* trophic phenomena alone occurred; and in scleroderma all three of the signs mentioned were present, as they were in Dr. Armstrong's patient. Dr. Hurley said that some years previously in his out-patient clinic he had seen a patient with a very similar condition, but it was bilateral. Cervical sympathectomy was performed on one side, and there was no doubt that subsequently the side operated on was much better than the side not operated on. The cause of scleroderma was unknown, but it was ascribed to disturbances of the ductless glands. In treatment the administration of thyreoid gland was most popular, but in certain selected cases big doses of pituitary gland preparations had been of some value.

DR. A. E. COATES said that Dr. Hurley's suggestion was of some interest, but he thought that Dr. Armstrong's patient was one of those whose condition could not be classified in any of the well-known text-book categories. Some vascular disturbance and some lymphatic obstruction were present, and he wondered whether a specific or chronic infection had ever occurred; he had known of cases in which the scars of old tuberculous or syphilitic lesions had led to such an obstruction, and irritable phenomena in the neighbouring artery were not uncommon causes, as in the groin and axilla. The condition might have started off with some infective process, and it was his opinion that certain of these cases followed on old

tuberculous lesions. On that account he always felt chary about operating on patients who were not suffering from either clear-cut Raynaud's disease on the one hand or clear-cut Buerger's disease on the other. In the condition from which Dr. Armstrong's patient was suffering there must have been a considerable spasmodic element because of the recovery of the ulcers after sympathectomy. Scleroderma was more generalized, as a rule affecting all the extremities and the trunk. In Dr. Armstrong's patient, however, the condition was more focal and definite improvement had taken place. It should be borne in mind that the effects of periarterial sympathectomy were short-lived, but the period of five or six weeks of improvement after the operation was of value, as it gave time for an ulcer to heal or for a skin graft to take. As Dr. Armstrong had performed abdominal ganglionectomy after the periarterial sympathectomy, presumably the ulceration had recurred. The patient at the time of the meeting had the evidence of Horner's syndrome, which showed that the upper sympathectomy had been successfully carried out. Dr. Coates, like Dr. Armstrong, preferred for this operation the anterior approach of Royle. In the treatment of the lower extremity with removal of the lumbar sympathetic through an abdominal incision, a patient of his had died of paralytic ileus; since then he used the lumbar approach and avoided lifting the colon on the left side.

Dr. Coates congratulated Dr. Armstrong on the management of the case, because from the operative standpoint he had obtained a very successful and satisfactory result. With regard to the second patient whom Dr. Armstrong had mentioned, removal of the sympathetic had cleared up the condition, but Dr. Coates recalled that in the case mentioned there had been no evidence of Raynaud's disease elsewhere, and the reason for the development of the lesions was unexplained. In the absence of any other suitable treatment sympathectomy was justifiable in this case and had proved curative.

Dr. Armstrong, in reply, said that it had been suggested some years earlier that the patient's condition might be scleroderma; it was true that she had had recurrence of the ulceration after perivascular sympathectomy. On several occasions the blood serum had failed to yield the Wassermann reaction. She had been given thyreoid therapy earlier in life. The second patient to whom he had referred was at one time thought to have had a dressing of carbolic acid which was blamed for the first appearance of gangrene. The one thing that the two patients had in common was some endocrinal disturbance. The younger patient menstruated too frequenly and the older one suffered from irregular menstruation.

Dr. Hurley spoke again in answer to Dr. Coates and said that in scleroderma the changes occurred in the smaller and not in the palpable vessels, and the distribution of scleroderma was notably variable. It was true that it might be generalized, but in other cases various circumscribed areas only were affected.

Extensive Gout.

DR. A. E. DICKMANN showed a married man, thirty-five years of age, who was suffering from advanced gout. At the age of seventeen years the first acute attack of gout had affected both big toes, and since then he had had fresh attacks at an interval of approximately six months. For five years large tumours with soft spots had surrounded the joints, and, though he had not had much pain, he was crippled and had to walk on the outer sides of his feet. Six months before the meeting, after an acute attack, the mass on one foot broke down, discharging a substance which resembled horseradish sauce in appearance. Dr. Dickman curetted out of the cavity a large amount of chalky material and packed it with iodoform gauze. He asked for opinions as to what should be done for the other side. There was only a sinus left at the site of the operation, and the patient was able to walk on that foot now, but he had gouty masses elsewhere, for example, over the *tendo Achillis*, the tibial tuberosities and the olecranon processes, and gouty tophi were present on his ears. Otherwise the patient was particularly healthy. The patient's father was still living at the age of seventy-eight years, but when thirty years of age had got gout. The grandfather, too, was gouty, and both the father and the grandfather had retired at a comparatively early age from the police force on this account.

DR. S. O. COWEN said that this case should be discussed both from the orthopædic aspect and with reference to the treatment of gout. The latter subject was very interesting. Gout sometimes affected the external parts only or the internal organs only. In about 75% of cases external deposits of sodium biurate occurred without visceral lesions and without high blood pressure or nephritis. Some patients, however, developed visceral lesions. The gouty state arose as a disturbance of carbohydrate metabolism and was not so uncommon as was thought. Treatment was extremely difficult. Dietary restrictions did not have much effect on the deposits. Dr. Cowen referred specially to the use of "Atophan" in treatment. He doubted whether its use should be permitted; he knew of two deaths and of some other patients who, though they recovered, were in dire straits because of the administration of "Atophan". As a side effect it had some analgesic power and gave the patient some relief from pain; but Dr. Cowen doubted whether it was ever justifiable to use it. The changes in the liver brought about by "Atophan" were irreversible, and while some patients might get better, others died. There were two other types of drugs to consider. The salicylate group in general had the power of increasing the excretion of uric acid. Sodium salicylate or aceto-salicylic acid could be given at an interval of two weeks approximately, with the object of stimulating the uric acid excretion. The drugs of the colchicum group were of value, though certain patients continued to have acute attacks till they gave up drinking beer. It was of importance to know that the majority of preparations of the tincture or wine of colchicum were inactive, and Dr. Cowen had found personally that colchicine was much more satisfactory. Colchicum was used at times to exclude gout from the differential diagnosis; it was necessary to be sure that the preparation selected was active before it was used for this purpose. Dr. Dickmann's patient had told Dr. Cowen that in the early days he had discovered that beer rather than spirits precipitated trouble. Malted liquor was a potent cause in provoking attacks of gout. Something had to be done to bring back the patient's power of locomotion. In addition, Dr. Cowen recommended strict adherence to prescribed diet and complete abstention from alcohol, together with courses of sodium salicylate and occasionally of colchicine to keep the uric acid excretion going, though such treatment would not be efficacious in removing or melting away the tophi, but might stop the patient from losing ground.

DR. J. P. MAJOR said that "Atophan" was an extremely dangerous drug, as was the group that produced agranulocytosis, and a small dose had a dire effect on some people.

Dr. Dickmann, in reply, stated that the patient had been on a strict diet and sodium salicylate had been used. He said that he had made up his mind to operate on the other foot.

Pathological Specimens.

Dr. Dickmann also showed some specimens removed at autopsy from a patient whose history he recounted. He had operated on a woman for uterine prolapse of second degree, and also had removed the appendix and both Fallopian tubes. She stood the operation well and was taken to the ward, but did not come out of the anæsthetic properly, and treatment for shock was instituted. Next morning she was still unconscious, and a specimen of urine was found to contain considerable amounts of both sugar and albumin. On the third day she became restless and the left hand and arm were found to be paralysed; she also was unable to speak, though she appeared to understand what was said to her. There was no plantar extensor response or facial weakness; no abnormal eye signs were present. The sugar disappeared from the

urine on the fifth day after the use of insulin, but the patient died on the eighth day after operation. The specimens removed at autopsy had been prepared for demonstration, and it could be seen that there had apparently been an infarct involving about two inches of the right Rolandic area and one inch in Broca's area. In the specimen of the heart old vegetations could be seen on the aortic and mitral valves. The lungs were normal, but infarcts were present in the spleen and in the left kidney. Dr. Dickmann invited a discussion on this case.

DR. ERIC COOPER said that apparently the death was due to unrecognized subacute bacterial endocarditis and *endocarditis lenta*. It was not unknown that after an anæsthetic without cyanosis such a lesion might send off emboli. The vegetations on the heart were old and it would be of interest to ascertain their exact nature. The presence of multiple emboli excluded almost everything else from the diagnosis. Dr. Cooper had come across two such cases, both after thyreoidectomy, and he thought that the opening up of venous plexuses had something to do with it.

DR. C. J. O. BROWN sympathized with Dr. Dickmann because he had had a somewhat similar experience only last year. In his patient very large old vegetations were present on the tricuspid and aortic valves together with fresh accretions, and emboli were found in the lung, spleen and other organs. The sequence of events had been old-standing endocarditis with recent subacute bacterial exacerbation.

DR. W. A. HAILES said that he had also had a similar experience after thyreoidectomy with gas and oxygen anæsthesia. It had not been recognized that the patient had subacute bacterial endocarditis.

Bone Abscess in Neck of Femur.

DR. F. W. GRÜTZNER showed a little girl who had been admitted to hospital on November 18, 1936. The child's mother said that there had been pain in the region of the right hip, though the child stoutly maintained that there was no pain. She walked with a slight limp and had no other disability. The local doctor, when consulted, had referred the patient to the hospital. She looked healthy, and apart from the very slight limp no other abnormality was detected on examination. There was no family history of tuberculosis, and the chest was quite clear. On the day after the child's admission to hospital even the gait was normal; no Trendelenburg sign could be elicited and there was no tenderness and no wasting, though it was considered that slight limitation of most of the movements at the hip joint, equal on both sides, was present. A double Thomas splint was made for the child and she had been placed at rest on it. The wasting on the right side was greater than on the left, and in a skiagram taken shortly afterwards a small lesion was to be seen in the neck of the femur. In a later film the area of rarefaction had diminished and there was evidence of condensation. The temperature had been taken every four hours for a long time, but there had been no rise of temperature. The von Pirquet test gave a positive reaction and the lesion was considered for a time to be tuberculous. The patient had remained at rest for two months on a double Thomas splint, and from then had been allowed off it for increasing periods, commencing with one hour a day. The muscles had been massaged regularly and the patient had been given general tonic treatment, with attention to vitamins and calcium in the diet, and colloidal calcium had been injected intramuscularly. Dr. Grützner said that he would welcome suggestions as to diagnosis and further treatment.

DR. JOHN O'SULLIVAN, when asked to comment on the radiographic films, said that he thought that there was a low grade pyogenic infection present, such as a resolving coccal infection. There was a small sequestrum in the centre of a low grade abscess cavity. As this was a condition which was liable to retrogress, the progress should be watched by repeated skiagrams.

DR. PAUL JONES said that he too thought the process was a coccal one, though it was difficult to prove in such a case that the condition was not tuberculous; it might be either. He thought that a caliper splint could be used with a patten and crutches.

DR. ERIC COOPER asked Dr. Grützner to express an opinion as to what proportion of people in the district would be expected to give a positive von Pirquet reaction; he had noted that the child came from a little country town. Those tests could be used only in conjunction with a knowledge of local conditions.

Dr. Grützner, in reply, said that in his experience the incidence of positivity to human tuberculin was fairly high in the district.

NOMINATIONS AND ELECTIONS.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Hodge, Arthur Harold, M.B., 1935 (Univ. Sydney), 12, Butlers Road, Hurstville.

Varvaressos, Demetrios, L.R.C.P., L.R.C.S., 1937 (Edinburgh), L.R.F.P.S., 1937 (Glasgow), 61, Latimer Road, Bellevue Hill.

The undermentioned have been elected members of the New South Wales Branch of the British Medical Association:

Wheatley, Arthur, M.B., 1932 (Univ. Sydney), Warialda.

Richardson, Kenneth Stephen, M.B., B.S., 1931 (Univ. Sydney), 363, Rocky Point Road, Ramsgate.

The undermentioned has applied for election as a member of the South Australian Branch of the British Medical Association:

Richardson, Patricia Sophia, M.B., B.S., 1937 (Univ. Adelaide), Adelaide Hospital, Adelaide.

The undermentioned has been elected a member of the South Australian Branch of the British Medical Association:

Mackay, Margaret Eleanor, M.B., B.S., 1936 (Univ. Melbourne), Adelaide Hospital, Adelaide.

Medical Societies.

AUSTRALIAN ORTHOPÆDIC ASSOCIATION.

FORMS of application for active or associate membership of the Australian Orthopædic Association are now available and may be obtained from the Honorary Secretary, Dr. A. R. Hamilton, 135, Macquarie Street, Sydney.

Public Health.

POLIOMYELITIS.

THE following statement is made by the Infantile Paralysis Committee of New South Wales.

At the present stage of our knowledge of the intranasal instillation of chemicals in the prophylaxis of acute anterior poliomyelitis, the committee does not consider that it can recommend its general use in the event of an epidemic in the State of New South Wales.

Experimental work leaves little doubt that the virus of anterior poliomyelitis gains access to the body by the nasal cavity, invading the terminal processes of the olfactory nerves and passing up the axis cylinders to the brain and the spinal cord. If the entrance of the virus to the olfactory mucous membrane could be blocked, it might be possible to protect the central nervous system from invasion.

1. *Experimental Work*: Armstrong and Harrison (*United States of America Public Health Reports*, Volume LI, August 14, 1936, page 1105) found that a solution of picric acid and alum protected 20 monkeys against infection by poliomyelitis virus introduced into the nasal passages and which occasioned poliomyelitis in 16 out of 20 non-prepared controls. On the basis of this, they recommended its use in the human subject.

Schultz and Gerhardt (*Proceedings of the Society of Experimental Biology and Medicine*, Volume XXXV, January, 1937, page 524), in experiments on monkeys, showed that 1% zinc sulphate solution was more effective in protecting against poliomyelitis than was picric acid and alum solution.

Their conclusions were supported by Olitzky and Sabin (*Proceedings of the Society of Experimental Biology and Medicine*, Volume XXXVI, May, 1937, page 532).

Other substances tested were tannic acid, potassium alum, ferrous sulphate and colloidal iron. These were all found to be unsatisfactory, leaving zinc sulphate (1% solution) as the most effective protective substance in laboratory experiments on animals.

2. *Experience in the Prevention of Human Disease*: Armstrong (*American Journal of Public Health*, Volume XXVII, February, 1937, page 103) estimated that in an epidemic in Alabama, when the nasal passages of large numbers of people were sprayed, the relative incidence of poliomyelitis among sprayed and non-sprayed subjects was 16 : 21·7. It will be seen that this advantage is not great. This may have been due to the inadequate nature and duration of the spraying in a proportion of the subjects. The spraying included any kind of prophylactic and was not confined to the picric acid and alum solutions.

3. A member of the committee recently returned from abroad had the opportunity of discussing the clinical results with workers in America. She reports that the majority of these workers were not impressed with the results.

4. It was found that 20% of those treated suffered from headache, nausea and local irritation of the nose and throat. In this connexion there is no definite evidence that there is not a risk of permanent damage to the nasal mucous membrane and the sense of smell.

5. There is no evidence that results obtained in animals under experimental conditions in laboratories are reproduced in the human subjects under epidemic conditions.

6. Reviewing the work done, the committee is of the opinion that the general use of nasal spraying should not be advised until the results of further clinical trial are known.

R. B. Wade, Chairman.

The Infantile Paralysis Committee of New South Wales.

Correspondence.

POLIOMYELITIS.

Sir: Dr. Gilbert Phillips's letter in your issue of August 7 will no doubt raise the hope that a satisfactory and simple method of prophylaxis has been found in the intranasal instillation of 1% zinc sulphate, as recommended by Professor Peet.

Unfortunately there appear to be grave disadvantages in the general application of such a prophylactic measure. It is even possible that those who have been so treated have been deprived of the assistance of a valuable defensive mechanism against poliomyelitis.

The following extracts are from the article in *The Journal of the American Medical Association* of June 26, 1937, by Max M. Peet, Dean H. Echols and Harry J. Richter.[1]

> (*a*) The use of an atomiser with the ordinary tip introduced into the naris is of no value . . . . A special spray tip must be introduced to the region of the cribriform plate under direct vision . . . . It is not a procedure which can be applied by the parents or by a physician not familiar with intranasal work.
>
> (*b*) It was found that when zinc sulfate was actually applied to the olfactory area it produced a severe burning or smarting sensation with coryza and in most subjects a severe headache which lasted for several hours. . . . It was found that the local anæsthetic pontocaine hydrochloride, added to the zinc sulfate solution, would minimise and in many cases completely eliminate the discomfort that follows high instillations of 1% zinc sulfate alone . . . . A careful review of the literature fails to disclose any instance of pontocaine poisoning. The probabilities are that in a very wide application of this treatment individuals may be found who do have an idiosyncrasy to this anæsthetic.
>
> (*c*) Nasal douching . . . might be as effective in some children as a properly applied spray. However, it would require larger quantities of the solution with the probability that some of the anæsthetic would enter the accessory sinuses and pharynx with the possibility that the cough reflex might be abolished thus predisposing to pneumonia. The Proetz position with instillation of zinc sulfate by dropper may of necessity be used when small children are so uncooperative that insertion of the nasal spray tip is impossible. Under these circumstances the pontocaine is omitted.
>
> (*d*) When the solution has been properly applied to the upper nasal mucous membrane the sense of smell is temporarily lost, or at least impaired, but always returns to normal in a week to two weeks.

As Professor Peet recommends daily spraying for three consecutive days, then single sprays at intervals of two weeks, the sense of smell of any child treated according to his instructions would be lost for almost the whole period of an epidemic. The New South Wales epidemics of 1931-1932 and of 1934-1935 lasted for five months.

Armstrong and Harrison[2] have published experiments which appear to show that picric acid, which also has been used successfully as a prophylactic against poliomyelitis in the monkey, acts not as an antiseptic, but by virtue of its power to precipitate protein in the cells of the nasal mucosa. Neutral solutions were without effect, whereas acid solutions were protective. It seems probable that zinc sulphate also acts in this way. *The British Medical Journal*[3] of November 21, 1936, refers to Armstrong and Harrison's experiment in an article on the prevention of poliomyelitis. It stresses the opinion that a substance which is "conditioned for its efficacy by its capacity to coagulate protein and thus presumably to kill the cells in which the change is produced" should not be recommended for general use as a prophylactic measure without further knowledge of its ultimate effects.

The highest incidence of poliomyelitis recorded in any one year in New South Wales is 14·9 per 100,000 of population. In view of this low incidence it seems hardly justifiable to recommend the general use of a prophylactic measure which may cause permanent damage to the nasal mucous membrane.

When I was in New York three months ago I met many clinicians and research workers who were actively engaged in the campaign against poliomyelitis. None of these recommended the intranasal instillation of antiseptics as a method of prophylaxis.

The results of spraying with picric acid alum during the 1936 epidemic in Alabama[1] were not impressive. The incidence of poliomyelitis in the sprayed group as compared with the unsprayed was 16 : 21·7. Peet and his collaborators attribute this poor result to the use of an ordinary atomizer. Of the sprayed group, 20·8% complained of uncomfortable symptoms, such as headache, temporary nausea and irritation of throat and eyes. In the report of the experiment Armstrong says: "Had the applications of the chemicals been more uniformly thorough, more unpleasant consequences might have developed".

It is well to recall that in 1917 Amoss and Taylor[5] published the results of 56 experiments which showed that washings of the nasal and pharyngeal mucosa possess definite power to inactivate or neutralize the active virus of poliomyelitis, and that Flexner and Amoss[6] have made the following statement:

> The innate destructive property possessed by the nasal mucous membrane for the virus of poliomyelitis may be regarded as a valuable defensive mechanism. The question has often been raised whether, during an epidemic of poliomyelitis, the application of antiseptics to the nasal mucosa is to be recommended. In the case of chronic meningococcus carriers the suppression of that microorganism by the introduction of antiseptics directly into the nasopharynx has not been notably successful; and the meningococcus is apparently a much more fragile organism than the microbe of poliomyelitis.
>
> There is a further important consideration. Now that it has been shown that the nasal mucous membranes are themselves defensive, account needs to be taken of the action of antiseptic drugs upon the chemical substances in the membranes upon which their protective action depends.

Yours, etc.,

93, Macquarie Street, Sydney, August 12, 1937. KAREN HELMS.

References.

[1] Max M. Peet, Dean H. Echols and H. J. Richter: "The Chemical Prophylaxis for Poliomyelitis: The Technic of Applying Zinc Sulfate Intranasally", *The Journal of the American Medical Association*, Volume CVIII, June 26, 1937, page 2184.

[2] Charles Armstrong and W. T. Harrison: "Prevention of Intranasally Inoculated Encephalitis (St. Louis Type) in Mice and of Poliomyelitis in Monkeys by means of Chemicals Instilled into the Nostrils", *Public Health Reports*, Volume LI, August 14, 1936.

[3] "Prevention of Poliomyelitis" (Editorial Article), *The British Medical Journal*, November 21, 1936, page 1037.

[4] Charles Armstrong: "Experience with the Picric Acid-Alum Spray in the Prevention of Poliomyelitis in Alabama, 1936", *American Journal of Public Health*, February, 1937.

[5] H. L. Amoss and Edward Taylor: "Neutralization of the Virus of Poliomyelitis by Nasal Washings", *Journal of Experimental Medicine*, Volume XXV, 1917, page 507.

[6] Simon Flexner and H. L. Amoss: "Experiments on the Nasal Route of Infection in Poliomyelitis", *Journal of Experimental Medicine*, Volume XXXI, 1920, page 123.

Proceedings of the Australian Medical Boards.

VICTORIA.

A MEETING of the Medical Board of Victoria was held on July 7, 1937.

After consideration of the judgement upholding an appeal by Moritz Meyer, L.R.C.P. *et* S. (Edinburgh), L.R.F.P.S. (Glasgow), 1937, to a judge of the Supreme Court against the refusal of the Board to register him on the ground that there was no evidence that he had passed through a regular course of medical and surgical study of five or more years' duration within the meaning of the *Medical Act*, and of an opinion thereon obtained from counsel, it was resolved to recommend to the Chief Secretary that an application be made to the High Court for special leave to appeal.

An application by Eugene Sandner for the registration of the F.R.C.S. (Edinburgh), 1932, as an additional qualification was granted.

The name of Thomas Edwin George (Number 2879) was removed from the register pursuant to the provisions of Section 9 of the *Medical Act*, 1928.

The following deaths were reported: Number 2602, Donald Murray Ross; Number 3241, John Philip O'Brien; Number 2723, Roger St. Clair Steuart.

In reply to an inquiry by the Board, a letter was received from the General Medical Council stating that it was not the practice of the Council to fix a period of deregistration in cases of penal erasure from the register, it being preferred to deal with any application for restoration on its merits.

The Medical Council of India requested an early reply in regard to its proposal for the reciprocal recognition of medical qualifications. The secretary was instructed to inform the council that a decision would be made on receipt of information which the General Medical Council has been requested to supply in regard to the resumption of the recognition in the United Kingdom of diplomas granted by the University of Calcutta and the Punjab University.

The South Australian Medical Board communicated its decision to accept on a basis of reciprocity degrees of British Indian universities which are accepted by the General Medical Council.

With respect to an inquiry by the Medical Secretary, British Medical Association (Victorian Branch), as to the use of both "M.B., B.S." and "M.B., Ch.B." as abbreviations to describe the qualifications of bachelors of medicine and surgery of the University of Melbourne whose names appear in the register, it was decided to reply that it is the practice to insert in the register the accepted abbreviation signifying the diploma actually presented to the Board.

A certificate signed by a registered practitioner certifying that the top joint of a patient's thumb had been amputated and a radiograph showing that only the tip of the thumb had been removed were brought under notice. It was decided to request the practitioner concerned to wait on the Board at its next meeting and furnish an explanation.

Mr. R. V. Chapman, of Hawthorn, requested that an investigation be held into the alleged refusal of certain practitioners to reply to requests which he had made for information relating to the circumstances which attended the death of his mother in a hospital. Instructions were given that Mr. Chapman should be informed that, in the absence of particulars as to the names of the practitioners in question and other matters, the Board was not in a position to consider his request.

TASMANIA.

THE undermentioned have been registered, pursuant to the provisions of the *Medical Act*, 1918, of Tasmania, as duly qualified medical practitioners:

Mathew, Randolph Yule, M.B., B.S., 1933 (Univ. Melbourne), Commonwealth Laboratory, Launceston.
Retallick, Cyrus, L.R.C.S., L.R.C.P., 1896 (Edinburgh), L.R.F.P.S., 1896 (Glasgow), Derby.

Obituary.

ARTHUR MORITZ LAZARUS.

WE regret to announce the death of Dr. Arthur Moritz Lazarus, which occurred on August 11, 1937, at Melbourne, Victoria.

Books Received.

GASTROSCOPY: THE ENDOSCOPIC STUDY OF GASTRIC PATHOLOGY, by Dr. R. Schindler, with a preface by Dr. Walter Palmer; 1937. Chicago: The University of Chicago Press. Crown 4to, pp. 357, with 89 text-figures and 96 colour reproductions of gastroscopic observations. Price: $7.50 net.

Diary for the Month.

AUG. 23.—Australasian Medical Congress (B.M.A.): Fifth Session opens at Adelaide.
AUG. 25.—Victorian Branch, B.M.A.: Council.
AUG. 26.—South Australian Branch, B.M.A.: Branch.
AUG. 27.—Queensland Branch, B.M.A.: Council.
SEPT. 1.—Western Australian Branch, B.M.A.: Council.
SEPT. 1.—Victorian Branch, B.M.A.: Branch.
SEPT. 2.—South Australian Branch, B.M.A.: Council.
SEPT. 3.—Queensland Branch, B.M.A.: Branch (Jackson Lecture).
SEPT. 7.—New South Wales Branch, B.M.A.: Organization and Science Committee.
SEPT. 10.—Queensland Branch, B.M.A.: Council.
SEPT. 14.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
SEPT. 15.—Western Australian Branch, B.M.A.: Branch.
SEPT. 21.—New South Wales Branch, B.M.A.: Ethics Committee.

Medical Appointments.

Dr. R. Y. K. Mathew has been appointed Acting Chief Quarantine Officer (General) of Tasmania, under the provisions of the *Quarantine Act*, 1909-1924.

* * *

Dr. J. D. Fotheringham has been appointed Resident Medical Officer at the Adelaide Hospital, Adelaide, South Australia.

* * *

Professor F. Goldby has been appointed Honorary Consulting Anatomist at the Adelaide Hospital, Adelaide, South Australia.

* * *

Dr. E. B. Tunbridge has been appointed Medical Officer of Health to the Augusta-Margaret River Road Board, and Dr. T. M. Gilbert Medical Officer of Health to the Cue District Road Board, pursuant to the provisions of *The Health Act*, 1911-1935, of Western Australia.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser", pages xviii to xxi.

BALMAIN AND DISTRICT HOSPITAL, BALMAIN, NEW SOUTH WALES: Junior Resident Medical Officer.
DEPARTMENT OF PUBLIC HEALTH, PERTH, WESTERN AUSTRALIA: Resident Medical Officer.
DEPARTMENT OF PUBLIC INSTRUCTION, MELBOURNE, VICTORIA: Medical Officer.
DEPARTMENT OF PUBLIC HEALTH, MELBOURNE, VICTORIA: District Health Officer.
LEWISHAM HOSPITAL, LEWISHAM, NEW SOUTH WALES: Honorary Officers.
PUBLIC SERVICE BOARD, ADELAIDE, SOUTH AUSTRALIA: Medical Inspector of Schools.
QUEEN VICTORIA MEMORIAL HOSPITAL, MELBOURNE, VICTORIA: Resident Medical Officer.
ROYAL PRINCE ALFRED HOSPITAL, SYDNEY, NEW SOUTH WALES: Honorary Officers.
SAINT MARGARET'S HOSPITAL FOR WOMEN, SYDNEY, NEW SOUTH WALES: Honorary Officers, House Surgeon.
THE TOOWOOMBA HOSPITALS BOARD, TOOWOOMBA, QUEENSLAND: Resident Medical Officer.
VICTORIAN EYE AND EAR HOSPITAL, MELBOURNE, VICTORIA: Resident Surgeons.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment referred to in the following table without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCHES.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17.	Brisbane Associate Friendly Societies' Medical Institute. Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY Hospital are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.
SOUTH AUSTRALIAN: Secretary, 178, North Terrace, Adelaide.	All Lodge appointments in South Australia. All contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 205, Saint George's Terrace, Perth.	All Contract Practice Appointments in Western Australia.

Editorial Notices.

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